Exhibit 1

First Regulatory Science Doctorate at USC

BY **Kukla Vera** APRIL 21, 2008

Recall of Heparin, a widely used blood thinner, due to contaminants in shipments from in China .... Lead in paint on toys prompts massive toy recalls .... Wires used in implantable heart devices are defective and recalled by the manufacturer.

Classes will be offered at the USC Health Sciences campus and via distance education, Richmond said.

Photo/Lee Salem

These are just a few recent headlines that have scared consumers, creating an uncertainty in the integrity of the foods we eat, the medicines we take and the medical devices we use.

In order to make products safer while following government regulations, USC announced the world's first program leading to a professional doctorate in regulatory science at the 2008 Horizons Conference of the Regulatory Affairs Professional Society in San Francisco.

"The doctoral program is aimed at mid-career executives in the rapidly growing biomedical and pharmaceutical industries," said Frances J. Richmond, the director of the program. "It will focus on global strategies for dealing with the explosion of new health care products and the web of national laws and international policies that govern everything from clinical trials to manufacturing and advertising."

Richmond started the USC regulatory science program offering a Master of Science curriculum in 1999. At its inception, the USC program was one of only a handful in the nation, though today a dozen programs exist.

USC's program has grown from a few students to nearly a hundred. The demand for the graduates has been startling, with many entertaining multiple job offers upon or before degree completion.

"Dr. Richmond has cultivated a rich network of industry partners, many of whom teach in the program and hire our graduates. These partners convinced us of the need to offer the professional doctorate," said School of Pharmacy Dean R. Pete Vanderveen.

According to Richmond, regulatory science is transitioning from administering paperwork and procedures to pioneering new ways to manage the opportunities and challenges that have been the fodder of news headlines over the past years.

“The USC professional doctoral program in regulatory science represents a major milestone in recognizing the critical importance of regulatory affairs as a discipline requiring the highest level of formal scientific training,” said Rick Wilson, senior vice president of Global Regulatory Affairs at the pharmaceutical company Allergan.

“Just as the master’s program has produced critically needed talent for this important field, the doctoral program promises to increase the supply of well-trained, knowledgeable persons needed for industry, academia and regulatory agencies.”

Added Richmond, “Classes for students in the doctoral program will be offered at the USC Health Sciences campus and via distance education classes that provide a virtual classroom experience through lecture webcasting, live video-conferencing and ‘e-teams’ tackling simulated projects. The program structure has been designed to accommodate working professionals.”

The program is expected to take three to five years, depending on the student’s prior education and the amount of time available to devote to studies.

Each student’s studies will culminate with the development and defense of an original research thesis in an area at the forefront of this emerging new science. Recognizing the growing shortage of regulatory science professionals, it is anticipated that many companies will provide substantial support for students who enroll in the program.

Applications are currently being accepted for the inaugural class starting this fall.

For more information, contact regsci@usc.edu or Kathy Knodel, manager of regulatory science programs, at (323) 442-3102.

Top stories on USC News

Health

Physical spaces where kids live, play and learn have big impact on obesity, eating behaviors

USC study identifies the strongest environmental predictor of childhood and adolescent obesity.

Health

Clinical trial investigating innovative way to control Type 2 diabetes

Study examines if an outpatient, nonsurgical endoscopic procedure can help patients stabilize blood glucose levels without the need for medication or insulin.

University

Notable USC alums to receive honors at 47th annual Black Alumni Association Scholarship Benefit

Daniel Prince will receive the 2023 Black Alum of the Year Award. Miki Turner and Kiesha Nix also will be recognized.

Exhibit 2

PROGRAMS & COURSES | SPEAKERS & ADVISORS | APPLY | PROGRAM RESOURCES | GET ANSWERS | DISTANCE COURSES

PROGRAMS & COURSES

SECTIONLINKS

Doctor of Regulatory Science (DRSc)

A doctorate designed specifically for Regulatory Professionals!

The University of Southern California is pleased to announce the launch of its new professional doctorate program in Regulatory Science (DRS). Regulatory Science addresses the art and science of developing medical products and foods through the complex regulatory and reimbursement paths required to market such product internationally. The proposed 64-unit professional doctorate is a novel, specialized program of study that cultivates research, leadership and inquiry skills for advanced students in the emerging profession of global regulatory science. It is designed to produce graduates who have a particular expertise in strategic management, policy development and research assessment and who will work in senior positions in the public sector, academia and the medical products industry. Participants in this program will take a set of interdependent courses that extend from a strong core of basic regulatory science coursework and additionally focus on three main areas—global product strategy, product lifecycle strategy, and project and personnel management. Students admitted with advanced standing after foundational coursework at the MS level will participate as a cohort that typically has a two-year cycle of classes and an additional year of dissertation development. The program has been designed to meet the needs of individuals who are already working full-time outside of the university in positions in which they have substantial leadership or managerial responsibilities. The doctoral degree will be administered by the School of Pharmacy. For more information see our website, regulatory.usc.edu, or discuss the program with our program manager, at 323-442-3102, regsci@usc.edu.

Related Article on USC's DRSc Program:
First Regulatory Science Doctorate at USC by Kukla Vera (April 2008)

Why a Doctorate in Regulatory Science?

Foods, drugs and medical devices have been regulated for more than a century. In the last decade, however, we have seen dramatic change in the level of preparation needed for effective management in this sector. Societal concerns over safety, globalization and technological innovation have increased the amount and detail of administrative law in the US and other areas of the world. At the same time, the increased sophistication of medical products has driven out the generalist; now regulatory leadership depends on a constellation of skill sets in science, law and management. Individuals who will lead the regulatory teams of the future must possess critical thinking skills and research acumen to be able to evaluate their own product and position it in a crowded marketplace. At the same time, they must possess a strong knowledge of policy and law, and must be able to work with large and diverse teams of individuals with different specializations and work cultures. In a recent market survey in which industries were asked what were the skill sets that need to be developed in regulatory leaders, attention was drawn to three types of capabilities: outstanding people and project management skills, a good capability to understand and work within transnational organizations to make globally relevant decisions, and a broader knowledge of policy and business than is typically acquired at junior and midlevels of the regulatory career structure. A further pressing problem is the graying of the current high-level regulatory professional. Most of the current leadership in Regulatory Science comes from individuals on the verge of retirement. These individuals learned on-the-job slowly as the regulations developed and now are leaving the field; the next generation of leaders will not have the same luxury.

Up to the present, a number of MS programs in Regulatory Science have been developed, but these are designed to educate practitioners in early career stages. What is needed now is a more advanced program that generates leaders equipped with tools and knowledge appropriate to individuals in the upper echelons of the profession where they command many subordinates and take responsibility for decisions that steer policy or company strategies. Our interest in developing the first US professional doctoral degree in Regulatory Science responds to requests made to us both from industries who are interested in recruiting and further training regulatory talent and from the professional organizations in this sector who see a strong need for strategic and research training to support policy and business decision-making. Like other professional doctorate degrees in education and policy studies, our goal is to develop individuals who can serve as leaders. However, in this case, those leaders are needed as a part of the health care system, where they will oversee the development and commercialization of medical devices, pharmaceuticals and foods, and will lead companies and government agencies concerned with regulatory planning and policy. These are the individuals who will replace the previous generation of regulatory experts, but they must be broader than most current experts. The products that they will foster, and the culturally and economically diverse countries in which they must operate, present a paradigm shift of a kind that this industry has not seen before. If we are to assure that new technologically sophisticated products make it to the marketplace, we must find new ways of benchmarking best practices and shortening the critical path that now exceeds a decade for most innovative pharmaceuticals and devices.

Our vision is coherent with that of the NIH and FDA whose Roadmap Initiative and Critical Path activities stem from strong concern about the ability to sustain growth in this sector using old methods.

What is the admissions process?

Students entering the DRS program must complete 64 units of specified coursework. Students will typically take a series of courses that are foundational for both the MS and DRS degree. Most students will enter after first registering in the MS Regulatory Science program. After taking a minimum of 15 units in Regulatory Science, students with good academic standing and strong leadership skills will be allowed to apply to the doctoral program. Students from the MS (Regulatory Science) program can use the credits earned in the MS program toward their subsequent requirements in the doctoral program. Also eligible for the doctoral program are students who have already taken graduate studies elsewhere either in Regulatory Science or complementary program. Students entering as advanced placement students can apply relevant units from their previous MS studies toward the doctoral program according to the transfer of credits rules of USC. Students who do not come from an MS program in Regulatory Science must be prepared to take supplementary courses in order to ensure that their foundational regulatory background is adequate. This will be ascertained on an individual basis according to evaluations by the selection committee and recommendations of the advisory committee for that student. Most students will take the courses that are listed in the sample student program below, but if students have strong previous experience in some area of study, other appropriate graduate courses may be substituted with the permission of the program director.

What must I do to graduate?

Students will take a written examination after they complete the foundational courses.. The doctoral degree will typically be completed within 5 years of entry from the beginning of the program. Students will be monitored throughout the program on a term by term basis to ensure that they maintain an appropriately high GPA of 3.0 or above; failure to maintain this GPA for two consecutive terms will normally result in dismissal from the program. By the end of the program, we anticipate that the students will not only have a mature and detailed understanding of the regulations underlying global regulatory affairs, but a strong understanding of managerial tools, policy setting mechanisms and strategic decision making in the medical products and foods sectors. In addition, they should understand the basic tenets of research and analysis as evidenced by their thesis submission, which will be typically focused on policy, best-practices or organizational management. Graduation depends upon the successful completion of coursework with a minimum GPA of 3.0, and the successful defense of a dissertation.

How will the program be structured?

The program is organized as a series of modules with different foci. Students must take a minimum number of credits in each focus, and then can add additional elective courses from a broader portfolio of appropriate offerings taught in the School of Pharmacy and other Schools in the University. We encourage students to take at least a few courses in other Schools so that they develop a broader perspective and interdisciplinary appreciation, but aim to offer a sufficient richness of courses to meet the needs of our doctoral students within our School, should timetabling issues preclude the option of courses outside of the School of Pharmacy that might be given only during the normal working week.

- **Foundational courses in Regulatory Science** (minimum 15 units): These form the base and would typically be composed of core courses to the MS program or equivalent courses from graduate programs elsewhere.

- **Product Lifecycle Strategy** (minimum 8 units): A number of courses in this grouping are offered by the School of Pharmacy, either through Regulatory Science or through the Titus Family Department of Clinical Pharmacy and Pharmaceutical Economics and Policy. Students are also encouraged to take courses outside of the Pharmacy School when more specialized courses fit their personal research or professional plans.

- **Project and Personnel Management** (minimum 8 units): Relevant courses are available through the Regulatory Science program. Alternative options are available from other University of Southern California Schools including the Marshall School of Business and School of Policy, Planning and Development.

- **Global Regulatory Strategy and Policy** (minimum 8 units): Globally-oriented courses. Two of these courses take students abroad, so that participants can meet global regulatory leaders and study global health-care systems in a challenging and immersive cultural experience.

- **Research and dissertation preparation and completion** (10+ units): All students will complete a professional dissertation that starts with at least one course in research design. We currently offer two such courses, one in basic/social sciences methodology and the other in clinical study methodology. Students must take at least one of these courses in preparation for their dissertation research. Research will be concerned with specific aspects of regulatory science, such as policy, administration, best practices or ethics. The students will work in subgroups of 3-4 as they develop their research projects, and will meet regularly in this group with their advisory team to discuss progress and challenges. Each student will be mentored by two identified advisors, one from university graduate faculty and the other an industry or government supervisor/mentor who normally is appointed as an adjunct in the School. Each student must produce and defend an independent dissertation as a requirement of graduation.

Program Requirements

1. Baccalaureate or graduate degree in an appropriate discipline. Applicants must provide transcripts of colleges/universities attended. Applicants with foreign transcripts must submit an official language transcript as well as a certified translation.

2. Proficiency with the English language and excellent communication skills.

3. Three letters of reference highlighting leadership skills in industry.

4. One page letter statement of purpose- (ie. "Why do you want to take the degree in Regulatory Science?", "What attributes do you have that distinguish you as a good candidate for our program?")

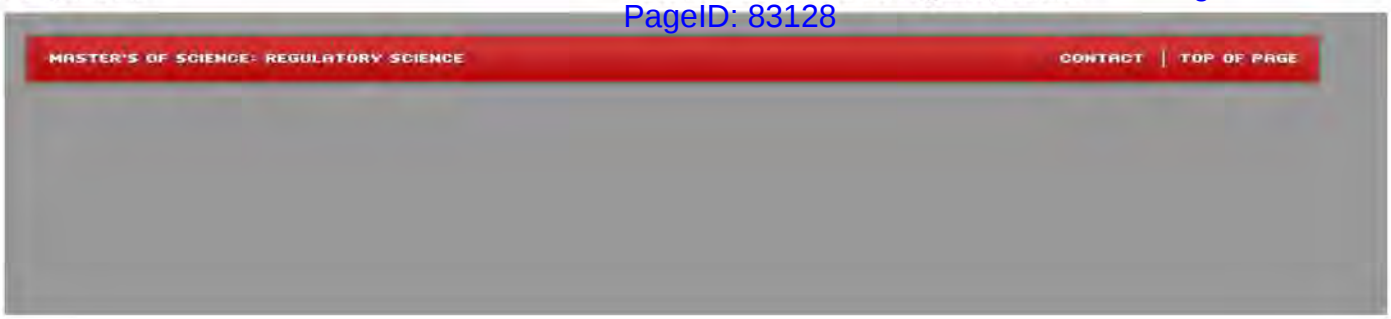
MASTER'S OF SCIENCE: REGULATORY SCIENCE
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Exhibit 3

KGI
KECK GRADUATE INSTITUTE

Clinical and Regulatory Affairs

Program Director: Susan Bain, DRSc (http://www.kgi.edu//web/20150322212732/http://www.kgi.edu/faculty-and-research/profiles/susan-bain.html)

Every drug, diagnostic test and medical device sold in the United States must meet a rigorous set of criteria to ensure quality and performance requirements. These standards are imposed by federal law and overseen by the Food and Drug Administration. Similar agencies regulate new product approvals in other countries. Although the process can be lengthy and expensive, patients needing medications and devices are relatively certain they are receiving safe, effective products of reliable quality. FDA monitoring continues even after these products have been approved for sale insuring that as more people use the product, issues such as appearance of rare side effects will be understood.

Topics in the Curriculum

Clinical Development: Phases 1-3 Studies
Accelerated Drug Approvals, Accessibility Programs
Biostatistics
Small Molecule Formulation
Clinical Trials Design
Drug Delivery Systems
Drug Master Files (DMF)
Good Clinical Practices (GCP)
Investigational New Drug Application (IND)
Common Technical Document (CTD)
Labeling, Packaging and Advertising
New Drug Application (NDA)
Post-approval Changes, Phase 4 Studies
Action letters and Pre-Approval Inspections (PAI)
Orphan Drug Development Program
International Regulatory Affairs
Standard Operating Procedures (SOPs)

Course Offerings for the Clinical and Regulatory Affairs Major

Eighteen units are required for the Clinical and Regulatory Affairs major.

Required (12.0)
ALS 418 Biopharmaceutical Quality Assurance and Control (http://www.kgi.edu/current-students/academic-affairs/course-catalog/courses/als-418.html) (1.5 units)
ALS 419 Chemistry, Manufacturing, and Controls Regulation of Pharmaceuticals (http://www.kgi.edu/current-students/academic-affairs/course-catalog/courses/als-419.html) (1.5 units)
ALS 433 Design of Clinical Trials (http://www.kgi.edu/current-students/academic-affairs/course-catalog/courses/als-433.html) (1.5 units)
ALS 434 Clinical Biostatistics (http://www.kgi.edu/current-students/academic-affairs/course-catalog/courses/als-434.html) (3.0 units)
ALS 435 Medical Device Regulatory Affairs (http://www.kgi.edu/current-students/academic-affairs/course-catalog/courses/als-435.html) (1.5 units)
ALS 439 Drug and Biologic Regulations (http://www.kgi.edu/current-students/academic-affairs/course-catalog/courses/als-439.html) (1.5 units)
ALS 464 European Regulatory Affairs (http://www.kgi.edu/current-students/academic-affairs/course-catalog/courses/als-464.html) (1.5 units)

Elective

ALS 401 Biotechnology-based Therapeutics (http://www.kgi.edu/current-students/academic-affairs/course-catalog/courses/als-401.html) (3.0 units)

ALS 432 Writing an Orphan Drug Application (http://www.kgi.edu/current-students/academic-affairs/course-catalog/courses/als-432.html) (1.5 units)

ALS 437 Clinical Pharmacology I (http://www.kgi.edu/current-students/academic-affairs/course-catalog/courses/als-437.html) (3.0 units)

ALS 438 Clinical Pharmacology II (http://www.kgi.edu/current-students/academic-affairs/course-catalog/courses/als-438.html) (3.0 units)

ALS 443 Supply Chain and Biotech Operations (http://www.kgi.edu/current-students/academic-affairs/course-catalog/courses/als-443.html) (1.5 units)

Exhibit 4

KGI
KECK GRADUATE INSTITUTE

Susan Bain, DRSc

Professor of Practice, Clinical, Regulatory and Quality; Program Director, MBS in Clinical and Regulatory Affairs

Areas of Expertise
Regulatory Affairs, Quality Assurance, Compliance and Operations

About (https://web.archive.org/web/20150316121634/http://www.kgi.edu/faculty-and-research/profiles/susan-

Courses (https://web.archive.org/web/20150316121634/http://www.kgi.edu/faculty-and-research/profiles/susan-bain.html#!/courses)

ALS 362	**Introduction to US Food and Drug Law (http://www.kgi.edu/current-students/academic-affairs/course-catalog/courses/als-362.html)** This course will provide students with broad general competencies in regulatory affairs for all FDA-regulated product classes (drugs, biologics and devices) throughout the product lifecycle (pre-clinical development, clinical development and post marketing).
ALS 433	**Design of Clinical Trials (http://www.kgi.edu/current-students/academic-affairs/course-catalog/courses/als-433.html)** This course will provide students with a more in-depth understanding of clinical trial design, conduct and strategy for therapeutic products.
ALS 435	**Medical Device Regulatory Affairs (http://www.kgi.edu/current-students/academic-affairs/course-catalog/courses/als-435.html)** This course examines the operational, strategic and commercial aspects of the regulatory approval process for new medical devices, biologics, and combination products in the United States.
ALS 439	**Drug and Biologic Regulations (http://www.kgi.edu/current-students/academic-affairs/course-catalog/courses/als-439.html)** This course will provide students with an in-depth understanding of relationships between scientific discovery, testing and regulatory oversight of drug and biological medical products.
ALS 464	**European Regulatory Affairs (http://www.kgi.edu/current-students/academic-affairs/course-catalog/courses/als-464.html)** This course will provide students with a broad background and understanding of the most current European Union regulatory requirements, strengthening their capacity to discuss, perform and address the regulatory requirements effecting licensure of products from the pharmaceutical and medical device industries.

Exhibit 5

KGI
KECK GRADUATE INSTITUTE

ALS 362: Introduction to US Food and Drug Law

Course Number: ALS 362
Course Name: Introduction to US Food and Drug Law
Year: First-year
Semester: Fall/Spring
No. Units: 1.5
Faculty/Instructor(s): Susan Bain (http://www.kgi.edu/x12768.xml)

Description

This course will provide students with broad general competencies in regulatory affairs for all FDA-regulated product classes (drugs, biologics and devices) throughout the product lifecycle (pre-clinical development, clinical development and post marketing). Emphasis will be placed on regulatory interactions – submissions, other communications and inspections – for each product class and for each phase of the product lifecycle.

Topics Covered

- History of FDA and Food, Drug and Cosmetic Law
- General principles in regulatory submissions, FDA communications and meetings
- Good Clinical Practice
- Prescription Drug Submissions: INDs and NDAs
- Generic Drug Submissions
- Over the counter drug products
- Drug labeling, advertising and promotion
- Post-marketing and pharmacovigillance of drugs, biologics and devices
- Special issues in Biologics submissions
- Other product classifications: combination products, cells and tissues, veterinary products
- PDUFA
- ICH
- Orphan drug development and regulation
- FDA inspection and enforcement activities

Required Texts

Click here for required texts.
(https://web.archive.org/web/20150322013532/http://www.bkstr.com/webapp/wcs/stores/servlet/booklookServlet?bookstore_id-1=994&term_id-1=FA2012&div-1=KG&dept-1=ALS&course-1=462&Section-1=01)

Exhibit 6

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ALS 439: Drug and Biologic Regulations

Course Number: ALS 439
Course Name: Drug and Biologic Regulations
Year: Second-Year
Semester: Spring
No. Units: 1.5
Faculty/Instructor(s): Susan Bain (http://www.kgi.edu/x12768.xml)

Description

Drug and Biological medical products are among the most profitable, yet most demanding to commercialize, requiring the major regulatory oversight. This course will provide students with an in-depth understanding of relationships between scientific discovery, testing and regulatory oversight of drug and biological medical products. It will look at the practical issues and rules governing prescription and over-the-counter drugs, and look at the changes that being introduced by genetic engineering, generic and biological product development. This course will consider the issues facing regulatory specialists as they work with the FDA and other international regulatory bodies to secure and maintain product approval.

Exhibit 7

‹ DOCTORATE IN REGULATORY SCIENCE (HTTPS://PHARMACYSCHOOL.USC.EDU/PROGRAM/DOCTORATE-IN-REGULATORY-SCIENCE/)

Frequently Asked Questions

What is regulatory science? ()

Regulatory Science relates the regulatory and legal requirements of biomedical product development to the scientific research needed to ensure the safety and efficacy of those products. It is an emerging profession experiencing tremendous growth. The rapid expansion of the biomedical industry has resulted in a particularly large and unmet demand for regulatory professionals. The Master of Science in Regulatory Science is an intensive, interdisciplinary program within the school designed to produce graduates whose backgrounds in biological, pharmaceutical, and biomedical sciences are enhanced by the knowledge and skills needed to manage regulated biomedical products. You can also read an FDA article “Why You Should Care About Regulatory Science (http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm317070.htm).”

What career paths are open in the fields of regulatory science and drug development? ()

What is included in the graduate level curriculum? ()

Am I eligible to apply to the program? ()

What are your admission cycles? ()

Can I take a course or two before applying to see if the program is right for me? ()

Can I work while earning my regulatory science degree at the same time? ()

How long will I typically take to earn a degree in regulatory science? ()

What is the difference between a doctorate and a PhD in regulatory science? ()

Do you have distance learning courses available in your program? ()

Do you offer a dual degree program with regulatory science? ()

What is the cost of tuition for the program? ()

Is financial aid and/or scholarships available? ()

SCHOLARSHIPS (HTTPS://PHARMACYSCHOOL.USC.EDU/DEPARTMENTS/REGULATORY-QUALITY-SCIENCE-DEPARTMENT/SCHOLARSHIPS/)

Contact

Desirae Hernandez

Program Manager – Admissions and Professional Development
regsci@usc.edu (mailto:regsci@usc.edu)
(323) 442-0631

APPLICATION PORTAL NOW OPEN (https://usc.liaisoncas.com/applicant-ux/#/login)

Exhibit 8

< REGULATORY SCIENCES PROGRAMS (HTTPS://PHARMACYSCHOOL.USC.EDU/DEPARTMENTS/REGULATORY-QUALITY-SCIENCE-DEPARTMENT/#REGSCIPROGRAMS)

MS in Medical Product Quality

The STEM designated Medical Product Quality degree is designed for students with a background in biological, pharmaceutical and biomedical sciences and biomedical engineering. The goal of the program is to train students in the theory behind current and future regulations which impact product quality, and to provide real-life practical tools they will use in their industry careers.

Professionals working in quality assurance and quality control are responsible for the testing and oversight required to ensure the safety of healthcare products. Students learn about the regulations and guidelines that ensure the quality of drugs, biologics and medical devices in the US and internationally, and how to apply this knowledge in the ever-expanding field of medical product development and manufacturing. They develop an understanding of the basic principles essential for the interpretation and implementation of quality practices and quality systems.

Courses are offered on weekends to accommodate working professionals and can be attended online for those looking to complete their studies from outside of the Los Angeles area. Students set their own pace, taking as many courses as they wish to take each semester.

Career support is offered to all students and alumni, including recruitment events, career fairs and regular distribution of job postings from companies nationally and internationally. Recruiters are aware of the reputation of our alumni, and are eager to hire our graduates.

SCHOLARSHIPS (HTTPS://PHARMACYSCHOOL.USC.EDU/DEPARTMENTS/REGULATORY-QUALITY-SCIENCE-DEPARTMENT/SCHOLARSHIPS/)

Contact

Desirae Hernandez

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APPLICATION PORTAL NOW OPEN (https://usc.liaisoncas.com/applicant-ux/#/login)

Exhibit 9

‹ DEPARTMENT OF REGULATORY AND QUALITY SCIENCES (HTTPS://PHARMACYSCHOOL.USC.EDU/DEPARTMENTS/REGULATORY-QUALITY-SCIENCE-DEPARTMENT/)

Courses

RSCI 506 Auditing Principles (3 Units, Fa)

The FDA and all regulatory agencies use inspections and audits to ensure the quality of health care products worldwide, particularly in order to maintain standards when manufacturing is outsourced abroad. Audits determine if companies comply with regulations set out in the Food, Drug and Cosmetic Act in the US or comparable requirements in other countries. The regulations set out requirements for companies to conduct internal audits of their own manufacturing, storage and distribution activities, including areas such as adverse event reporting, customer complaint handling and recall procedures. Regulatory agencies also use audits to ensure that companies conducting animal studies (GLP) and/or human clinical trials (GCP) comply with regulatory requirements. Students will be introduced to all aspects of auditing during the development and manufacturing of drugs, devices, dietary supplements and biologics.

Instructional Video **(https://www.youtube.com/watch?v=WExLtRqEj9s&ab_channel=USCDepartmentofRegulat**

RSCI 507 Quality Systems And Statistical Process Control (2 Units, Fa)

RSCI 508 Quality Assurance For Drugs And Biologics (3 Units, Sp)

RSCI 509 Quality Assurance For Medical Devices And Combination Products (3 Units, Sp)

MPTX 511 Introduction To Medical Product Regulation (3 Units, All)

MPTX 512 Regulation Of Pharmaceutical And Biological Products (3 Units, Sp, Su)

MPTX 513 Regulation Of Medical Devices And Diagnostics (3 Units, Su, Fa)

MPTX 514 Regulation Of Foods And Dietary Supplements (3 Units, Su)

MPTX 515 Quality Systems And Standards (3 Units, Su)

MPTX 516 Medical Products And The Law (3 Units, Fa)

MPTX 517 Structure And Management Of Clinical Trials (4 Units, Fa, Su)

MPTX 518 Writing Regulatory Drug Submissions (3 Units, Fa)

MPTX 519 Global Regulation Of Medical Products (3 Units, Sp)

RSCI 520 Introduction To Risk Management For Health Care Products (2 Units, Sp)

MPTX 522 Introduction To Clinical Trial Design And Statistics (3 Units, Sp)

MPTX 524 Introduction To Food Science And Technology (3 Units, Su [Odd Years])

MPTX 526 Chemistry Manufacturing & Controls (3 Units, Fa)

RSCI 527 Medical Product Safety (3 Units, Su [Even Years])

RSCI 529 Application Of Risk Management Tools And Techniques (2 Units)

RSCI 530 Translational Medicine: An Overview (2 Units)

RSCI 531 Industrial Approaches To Drug Discovery (4 Units, Sp)

RSCI 532 Early Stage Drug Development (3 Units, Su)

RSCI 533 Safety Evaluation During Drug Development (3 Units, Fa [Even Years])

RSCI 540 Analysis Of Food And Dietary Supplement Regulations (3 Units)

RSCI 541 Medical Product Development, Reimbursement, And Marketing (3 Units, Sp [Odd Years])

RSCI 590 Directed Research (1-12 Units, Maximum 12, All)

RSCI 599 Validation Requirements For Medical Products (2 Units, Sp [Odd Years])

RSCI 601 Biomedical Commerce (4 Units, Sp)

MPTX 602 Science, Research And Ethics (2 Units, Su Odd)

RSCI 603 Managing Complex Projects (3 Units, Sp)

RSCI 604 Regulatory Strategy In Asia (4 Units) – DRSc Course Only

RSCI 605 Managing Organizations And Human Resources (3 Units) – DRSc Course Only

RSCI 606 Regulation Of Emerging Technologies And Biological Products (3 Units, Fa [Odd Years])

RSCI 607 Theory, Methods And Practice Of Medical Products Research (4 Units) – DRSc Course Only

RSCI 608 Regulatory Strategy In Europe & The Americas (4 Units) – DRSc Course Only

MPTX 630 Directed Field-Research Project (6 Units, All)

Exhibit 10

‹ DEPARTMENT OF REGULATORY AND QUALITY SCIENCES (HTTPS://PHARMACYSCHOOL.USC.EDU/DEPARTMENTS/REGULATORY-QUALITY-SCIENCE-DEPARTMENT/)

Courses

RSCI 506 Auditing Principles (3 Units, Fa)

RSCI 507 Quality Systems And Statistical Process Control (2 Units, Fa)

RSCI 508 Quality Assurance For Drugs And Biologics (3 Units, Sp)

As the number of pharmaceuticals manufactured outside of the US increases, the FDA and other regulatory agencies must look at new ways to ensure their quality. Biologics are products derived from living sources including humans, animals and microorganisms. Biologics have seen significant international growth over the last few years. Since these products are synthesized from living organisms, ensuring the quality of biologics is especially complex. An essential tenet of regulatory oversight is the assurance of quality through post-marketing surveillance, internal audits and regulatory inspections. Students will learn about the regulations needed to ensure the quality of drugs and biologics in the US and internationally, and will gain an understanding of the principles necessary for the interpretation and implementation of a quality system.

RSCI 509 Quality Assurance For Medical Devices And Combination Products (3 Units, Sp)

MPTX 511 Introduction To Medical Product Regulation (3 Units, All)

MPTX 512 Regulation Of Pharmaceutical And Biological Products (3 Units, Sp, Su)

MPTX 513 Regulation Of Medical Devices And Diagnostics (3 Units, Su, Fa)

MPTX 514 Regulation Of Foods And Dietary Supplements (3 Units, Su)

MPTX 515 Quality Systems And Standards (3 Units, Su)

MPTX 516 Medical Products And The Law (3 Units, Fa)

MPTX 517 Structure And Management Of Clinical Trials (4 Units, Fa, Su)

MPTX 518 Writing Regulatory Drug Submissions (3 Units, Fa)

MPTX 519 Global Regulation Of Medical Products (3 Units, Sp)

RSCI 520 Introduction To Risk Management For Health Care Products (2 Units, Sp)

MPTX 522 Introduction To Clinical Trial Design And Statistics (3 Units, Sp)

MPTX 524 Introduction To Food Science And Technology (3 Units, Su [Odd Years])

MPTX 526 Chemistry Manufacturing & Controls (3 Units, Fa)

RSCI 527 Medical Product Safety (3 Units, Su [Even Years])

RSCI 529 Application Of Risk Management Tools And Techniques (2 Units)

RSCI 530 Translational Medicine: An Overview (2 Units)

RSCI 531 Industrial Approaches To Drug Discovery (4 Units, Sp)

RSCI 532 Early Stage Drug Development (3 Units, Su)

RSCI 533 Safety Evaluation During Drug Development (3 Units, Fa [Even Years])

RSCI 540 Analysis Of Food And Dietary Supplement Regulations (3 Units)

RSCI 541 Medical Product Development, Reimbursement, And Marketing (3 Units, Sp [Odd Years])

RSCI 590 Directed Research (1-12 Units, Maximum 12, All)

RSCI 599 Validation Requirements For Medical Products (2 Units, Sp [Odd Years])

RSCI 601 Biomedical Commerce (4 Units, Sp)

MPTX 602 Science, Research And Ethics (2 Units, Su Odd)

RSCI 603 Managing Complex Projects (3 Units, Sp)

RSCI 604 Regulatory Strategy In Asia (4 Units) – DRSc Course Only

RSCI 605 Managing Organizations And Human Resources (3 Units) – DRSc Course Only

RSCI 606 Regulation Of Emerging Technologies And Biological Products (3 Units, Fa [Odd Years])

RSCI 607 Theory, Methods And Practice Of Medical Products Research (4 Units) – DRSc Course Only

RSCI 608 Regulatory Strategy In Europe & The Americas (4 Units) – DRSc Course Only

MPTX 630 Directed Field-Research Project (6 Units, All)

Exhibit 11

‹ DEPARTMENT OF REGULATORY AND QUALITY SCIENCES (HTTPS://PHARMACYSCHOOL.USC.EDU/DEPARTMENTS/REGULATORY-QUALITY-SCIENCE-DEPARTMENT/)

Courses

RSCI 506 Auditing Principles (3 Units, Fa)

RSCI 507 Quality Systems And Statistical Process Control (2 Units, Fa)

RSCI 508 Quality Assurance For Drugs And Biologics (3 Units, Sp)

RSCI 509 Quality Assurance For Medical Devices And Combination Products (3 Units, Sp)

MPTX 511 Introduction To Medical Product Regulation (3 Units, All)

MPTX 512 Regulation Of Pharmaceutical And Biological Products (3 Units, Sp, Su)

MPTX 513 Regulation Of Medical Devices And Diagnostics (3 Units, Su, Fa)

MPTX 514 Regulation Of Foods And Dietary Supplements (3 Units, Su)

MPTX 515 Quality Systems And Standards (3 Units, Su)

If medical products fail, there can be life-threatening results. Quality assurance is a huge part of medical product development and constitutes a science in itself. In this introductory course, we will examine the way that different countries regulate the quality of medical products, from design and development to manufacturing and distribution. We will study the rules governing good laboratory and manufacturing practices, and explore how they mesh with ISO and European standards, CE marking and quality systems regulations. We will look at risk analysis and documentation, and participate in a real-life audit. Course requires a distance module to be completed by the last course date (allow two weeks minimum).

MPTX 516 Medical Products And The Law (3 Units, Fa)

MPTX 517 Structure And Management Of Clinical Trials (4 Units, Fa, Su)

MPTX 518 Writing Regulatory Drug Submissions (3 Units, Fa)

MPTX 519 Global Regulation Of Medical Products (3 Units, Sp)

RSCI 520 Introduction To Risk Management For Health Care Products (2 Units, Sp)

MPTX 522 Introduction To Clinical Trial Design And Statistics (3 Units, Sp)

MPTX 524 Introduction To Food Science And Technology (3 Units, Su [Odd Years])

MPTX 526 Chemistry Manufacturing & Controls (3 Units, Fa)

RSCI 527 Medical Product Safety (3 Units, Su [Even Years])

RSCI 529 Application Of Risk Management Tools And Techniques (2 Units)

RSCI 530 Translational Medicine: An Overview (2 Units)

RSCI 531 Industrial Approaches To Drug Discovery (4 Units, Sp)

RSCI 532 Early Stage Drug Development (3 Units, Su)

RSCI 533 Safety Evaluation During Drug Development (3 Units, Fa [Even Years])

RSCI 540 Analysis Of Food And Dietary Supplement Regulations (3 Units)

RSCI 541 Medical Product Development, Reimbursement, And Marketing (3 Units, Sp [Odd Years])

RSCI 590 Directed Research (1-12 Units, Maximum 12, All)

RSCI 599 Validation Requirements For Medical Products (2 Units, Sp [Odd Years])

RSCI 601 Biomedical Commerce (4 Units, Sp)

MPTX 602 Science, Research And Ethics (2 Units, Su Odd)

RSCI 603 Managing Complex Projects (3 Units, Sp)

RSCI 604 Regulatory Strategy In Asia (4 Units) – DRSc Course Only

RSCI 605 Managing Organizations And Human Resources (3 Units) – DRSc Course Only

RSCI 606 Regulation Of Emerging Technologies And Biological Products (3 Units, Fa [Odd Years])

RSCI 607 Theory, Methods And Practice Of Medical Products Research (4 Units) – DRSc Course Only

RSCI 608 Regulatory Strategy In Europe & The Americas (4 Units) – DRSc Course Only

MPTX 630 Directed Field-Research Project (6 Units, All)

Exhibit 12

‹ DEPARTMENT OF REGULATORY AND QUALITY SCIENCES (HTTPS://PHARMACYSCHOOL.USC.EDU/DEPARTMENTS/REGULATORY-QUALITY-SCIENCE-DEPARTMENT/)

Courses

RSCI 506 Auditing Principles (3 Units, Fa)

RSCI 507 Quality Systems And Statistical Process Control (2 Units, Fa)

RSCI 508 Quality Assurance For Drugs And Biologics (3 Units, Sp)

RSCI 509 Quality Assurance For Medical Devices And Combination Products (3 Units, Sp)

MPTX 511 Introduction To Medical Product Regulation (3 Units, All)

MPTX 512 Regulation Of Pharmaceutical And Biological Products (3 Units, Sp, Su)

MPTX 513 Regulation Of Medical Devices And Diagnostics (3 Units, Su, Fa)

MPTX 514 Regulation Of Foods And Dietary Supplements (3 Units, Su)

MPTX 515 Quality Systems And Standards (3 Units, Su)

MPTX 516 Medical Products And The Law (3 Units, Fa)

MPTX 517 Structure And Management Of Clinical Trials (4 Units, Fa, Su)

MPTX 518 Writing Regulatory Drug Submissions (3 Units, Fa)

MPTX 519 Global Regulation Of Medical Products (3 Units, Sp)

RSCI 520 Introduction To Risk Management For Health Care Products (2 Units, Sp)

MPTX 522 Introduction To Clinical Trial Design And Statistics (3 Units, Sp)

MPTX 524 Introduction To Food Science And Technology (3 Units, Su [Odd Years])

MPTX 526 Chemistry Manufacturing & Controls (3 Units, Fa)

RSCI 527 Medical Product Safety (3 Units, Su [Even Years])

RSCI 529 Application Of Risk Management Tools And Techniques (2 Units)

RSCI 530 Translational Medicine: An Overview (2 Units)

RSCI 531 Industrial Approaches To Drug Discovery (4 Units, Sp)

RSCI 532 Early Stage Drug Development (3 Units, Su)

RSCI 533 Safety Evaluation During Drug Development (3 Units, Fa [Even Years])

RSCI 540 Analysis Of Food And Dietary Supplement Regulations (3 Units)

RSCI 541 Medical Product Development, Reimbursement, And Marketing (3 Units, Sp [Odd Years])

RSCI 590 Directed Research (1-12 Units, Maximum 12, All)

RSCI 599 Validation Requirements For Medical Products (2 Units, Sp [Odd Years])

Regulated industries, such as medical product manufacturing, must adopt and adhere to complex compliance procedures to ensure their final product meets quality, safety and purity requirements so that it is safe for distribution and / or sale. As one of the essential pharmaceutical commercialization requirements, validation assures consistent reproduceable and repeatable results as part of the Quality Management System (QMS) for testing and manufacturing processes. In this course, we will follow the progression of the testing and manufacturing validation activities over time in the pharmaceutical industry, beginning with equipment qualification, computer system validation (CSV), cleaning validation, laboratory instruments, testing and methods validation, manufacturing process and environmental monitoring validation for accuracy and precision, security,

reliability, consistency and productivity. You will see how business concepts merge with project management and science, to assure and keep products safe and in compliance with applicable regulations.

RSCI 601 Biomedical Commerce (4 Units, Sp)

MPTX 602 Science, Research And Ethics (2 Units, Su Odd)

RSCI 603 Managing Complex Projects (3 Units, Sp)

RSCI 604 Regulatory Strategy In Asia (4 Units) – DRSc Course Only

RSCI 605 Managing Organizations And Human Resources (3 Units) – DRSc Course Only

RSCI 606 Regulation Of Emerging Technologies And Biological Products (3 Units, Fa [Odd Years])

RSCI 607 Theory, Methods And Practice Of Medical Products Research (4 Units) – DRSc Course Only

RSCI 608 Regulatory Strategy In Europe & The Americas (4 Units) – DRSc Course Only

MPTX 630 Directed Field-Research Project (6 Units, All)

Exhibit 13

2013 WL 4675377
Only the Westlaw citation is currently available.
NOT FOR PUBLICATION
United States District Court, D. New Jersey.

Sandra GEISS and Robert Geiss h/w, Plaintiffs,
v.
TARGET CORPORATION and/or Target Corporation of Minnesota, John Does 1–5 (fictitious persons) and ABC Corps 1–5 (fictitious corporations), Defendants/Third Party Plaintiff(s),
v.
Virtua Memorial Hospital, Virtua Memorial Hospital—Mt. Holly, Virtua West, John Does 1–10 (names unknown) and ABC Corps 1–10 (names unknown), Third Party Defendant(s).

Civil No. 09–2208 (RBK/KMW).
|
Aug. 30, 2013.

Attorneys and Law Firms

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OPINION

KUGLER, District Judge.

***1** This matter comes before the Court upon the motion of Target Corporation ("Target") for partial summary judgment, pursuant to Federal Rule of Civil Procedure 56, against Sandra and Robert Geiss ("Plaintiffs"). Virtua Memorial Hospital ("Virtua"), a third party defendant in this case, also now moves for summary judgment. For the reasons expressed herein, Target's motion for summary judgment is **DENIED.** However, Virtua's motion for summary judgment is **GRANTED.**

I. FACTS AND PROCEDURAL HISTORY

According to Plaintiffs, this matter arises out of a fall that Plaintiff Sandra Geiss sustained at a Target store in Burlington, New Jersey. Because Plaintiff's medical history and post-fall treatment are relevant to the conflicting theories of causation advanced by both parties, the Court will provide a detailed background to this case. Although the Court presents a composite of facts from Plaintiffs, Target, and Virtua, the Court will construe all facts in the light most favorable to the non-moving parties, as it must at this stage in the litigation.

In January 2006, Plaintiff underwent knee replacement surgery in which her right knee joint was removed and replaced with a prosthetic component. Target's Mot. Summ. J., Ex. P–1 at 1. Plaintiff alleges that on July 25, 2007, she tripped over an uneven rug while passing through the entrance of the Burlington, NJ Target store, landing on her stomach and knees. *Id.,* Ex. B at 2; Target's Statement of Undisputed Material Facts ("SUMF"), ¶ 2. Plaintiff did not experience immediate pain on the day of her fall, but days later developed increasing pain in her right knee and required a cane and walker to ambulate. *Id.,* Ex. T at 33–40. On August 2, 2012, Plaintiff visited her primary care physician, Dr. Chatyrka, complaining of right knee pain. Target's SUMF, ¶ 3. Dr. Chatyrka determined that Plaintiff was suffering from sciatica and recommended that she obtain an X-ray of her right knee. Target's Mot. Summ. J., Ex. C. The X-ray indicated that the prosthetic components were properly positioned and undamaged, but also revealed a fluid collection of unknown origin. *Id.,* Ex. D.

On August 17, 2012, Dr. Schoifet, the orthopedic surgeon who performed Plaintiff's knee replacement in 2006, examined Plaintiff's knee. *Id.,* Ex. E. Dr. Schoifet noted Plaintiff's complaints of increasing knee pain, but found that Plaintiff had no instability in her knee and confirmed that the X-ray demonstrated good positioning of the prosthetic components. *Id.;* Target's SUMF, ¶ 5–6. He ultimately concluded that Plaintiff suffered a right knee contusion as a result of her fall. *Id.*

On August 29, 2012, Plaintiff Sandra Geiss presented to Virtual Memorial Hospital complaining of "back pain, leg pain, numbness, pain radiating from back into legs and extreme pain when ambulating." Pls.' Supplemental Statement of Disputed Material Facts ("SDMF"), ¶ 7. A few hours after Plaintiff's arrival, tests revealed that Plaintiff had an elevated white blood cell count, elevated blood pressure, high blood sugar, and a high temperature. Target's Mot. Summ. J. at 4; *see also* Ex. F at 6–8. Soon thereafter, Plaintiff

was diagnosed with hypoxia and pneumonia. *Id.,* Ex. F at 9. Plaintiff was admitted to the hospital, and then to the Intensive Care Unit, where she was intubated. *Id.,* Ex. I at 2. Blood cultures also revealed that Plaintiff had MSSA (Methicillin–Sensitive Staphylococcus Aureus), a bacterial infection. *Id.* Plaintiff spent some time in the ICU in order to receive treatment for her various ailments and to stabilize her condition. *See* Pls.' Opp'n, Ex. A at 42–43. Dr. Lee does not recall exactly how long Plaintiff remained in the ICU. [1] *Id.* at 42–43.

***2** Much of the controversy in this case surrounds an "event" which allegedly occurred during Plaintiff's hospitalization. On September 25, 2007, an X-ray of Plaintiff's right knee revealed that her previously intact right knee prosthesis had subluxed (dislocated) by 3cm. Target's Mot. Summ. J., Ex. J. Plaintiff underwent emergency repair surgery on September 26, 2007, while her immune system was still compromised from the treatment of her other ailments. *Id.,* Ex. Q at 99–100. Despite the repair, Plaintiff subsequently developed an infection in her right knee requiring further treatment. Target's SUMF, ¶ 32. The infection persisted, which required doctors to remove the prosthesis and insert an antibiotic spacer. *Id.* at ¶ 33. Ultimately, Dr. Schoifet had to perform a "right knee arthrodesis," or fusion of Plaintiff's right knee. *Id.* at ¶ 34. Plaintiff's knee fusion has caused her significant pain, led to difficulty walking, and altered the range of activities in which she can participate. Dep. of Sandra Geiss at 90–94.

Although the subluxation was discovered on September 25, 2007, Plaintiff has no memory as to when or how it occurred. Target's Mot. Summ. J., Ex. T at 56–57. According to Plaintiff's expert, Dr. Gleimer, this subluxation occurred at some point while Plaintiff was hospitalized, but he cannot pinpoint a specific event, place or date. *Id.,* Ex. P–1 at 3. He does note, however, that the prosthetic is inherently stable and would not sublux on its own. *Id.* This confusion is enhanced due to a number of missing medical records. Specifically, Virtua cannot locate progress notes from August 29, 2007 to September 14, 2007, physician orders from September 4, 2007 to September 17, 2007, medical administration records from September 4, 2007 to September 19, 2007, and flow records from September 14, 2007, September 18, 2007 and October 3, 2007. Target's SUMF, ¶ 35. The Custodian of Records for Virtua, Jennfier Raio, attributes the loss of the records to human error. Virtua's Mot. Summ. J., Ex. D at 64–65.

On the basis of these events, Plaintiffs filed suit against Target on March 26, 2009 in the Superior Court of New Jersey, Burlington County. In the Complaint, Plaintiffs assert claims against Target for negligence and loss of consortium on behalf of Plaintiff Robert Geiss. Target was served on April 6, 2009. Within one month, Target properly moved the matter to this Court. On July 29, 2010, Target impleaded Virtua as a third party defendant in the case. In the Third Party Complaint, Target contends that Plaintiff's knee subluxation constitutes a superseding, intervening cause and that any injuries resulting therefrom are due solely to Virtua's negligence. Target seeks contribution and indemnification from Virtua for any damages for which Target may be liable to Plaintiffs in the underlying suit. Target's Third Party Compl., ¶ 11. Target also claims that it has been prejudiced by Virtua's failure to preserve all of Plaintiff's medical records and asserts a tort action for careless, negligent, and/or intentional spoliation of evidence, seeking contribution and/or indemnification as a remedy. *Id.* at 3–4.

***3** Both Virtua and Target now move for summary judgment. Target argues that Plaintiff's knee subluxation was neither actually nor proximately caused by Target's negligence. Target also contends that the expert opinion causally relating Plaintiff's fall at Target to her subsequent hospitalization should be barred as a net opinion. In its motion for judgment on the Third–Party Complaint, Virtua argues that neither party has adduced evidence supporting a prima facie case of negligence. Accordingly, Virtua asserts that there is no issue of material fact and that the hospital is entitled to judgment as a matter of law based on the current record.

II. STANDARD OF REVIEW

The court should grant a motion for summary judgment when the moving party "shows that there is no genuine dispute as to any material fact and that the movant is entitled to judgment as a matter of law." Fed.R.Civ.P. 56(a). An issue is "material" to the dispute if it could alter the outcome, and a dispute of a material fact is "genuine" if "a reasonable jury could return a verdict for the non-moving party." *Anderson v. Liberty Lobby, Inc. .,* 477 U.S. 242, 249, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986); *Matsushida Elec. Indus. Co., Ltd. v. Zenith Radio Corp.,* 475 U.S. 574, 587, 106 S.Ct. 1348, 89 L.Ed.2d 538 (1986) ("Where the record taken as a whole could not lead a rational trier of fact to find for the non-moving party, there is no 'genuine issue for trial.' ") (quoting *First National Bank of Arizona v. Cities Service Co.,* 391

U.S. 253, 289, 88 S.Ct. 1575, 20 L.Ed.2d 569 (1968)). In deciding whether there is any genuine issue for trial, the court is not to weigh evidence or decide issues of fact. *Anderson,* 477 U.S. at 248. Because fact and credibility determinations are for the jury, the non-moving party's evidence is to be believed and ambiguities construed in her favor. *Id.* at 255; *Matsushida,* 475 U.S. at 587.

Although the movant bears the burden of demonstrating that there is no genuine issue of material fact, the non-movant likewise must present more than mere allegations or denials to successfully oppose summary judgment. *Anderson,* 477 U.S. at 256. The nonmoving party must at least present probative evidence from which jury might return a verdict in his favor. *Id.* at 257. The movant is entitled to summary judgment where the non-moving party fails to "make a showing sufficient to establish the existence of an element essential to that party's case, and on which that party will bear the burden of proof at trial." *Celotex Corp. v. Catrett,* 477 U.S. 317, 322, 106 S.Ct. 2548, 91 L.Ed.2d 265 (1986).

III. DISCUSSION & ANALYIS

Target's Third Party Complaint seeks contribution and indemnification from Virtua for any liability that Target may face in Plantiffs' underlying action. If Target's motion is granted, Virtua's motion for summary judgment would be rendered moot. Therefore, it is prudent for the Court to first address Target's motion for summary judgment.

A. Target's Motion for Partial Summary Judgment

Target moves for summary judgment based on Plaintiffs' alleged failure to establish causation. Target argues that its alleged negligence was neither the actual nor proximate cause of Plaintiff's knee subluxation and the complications resulting therefrom. Target further posits that Plaintiff's knee subluxation was a superseding intervening cause which severs the causal chain of liability. Target also seeks to bar Dr. Gleimer's conclusion that "all hospitalizations subsequent to July 25, 2007 related to Ms. Geiss' knee, back or related infection or problems were caused by the fall at Target." *See* Target's Mot. Summ. J. at 31. Target argues that Dr. Gleimer's statement is a "net opinion," which is unsubstantiated by objective evidence. *Id.* The Court will address these arguments in reverse order, beginning with Target's challenge to Plaintiffs' expert.

a. Sufficiency of Expert Testimony

***4** Target challenges Dr. Gleimer's conclusion that all hospitalizations subsequent to July 25, 2007 are causally related to Plaintiff's fall at Target, arguing that it is a "net opinion" that is unsupported by the factual record. Admissibility of expert testimony is governed by Rule 702, which was amended in 2000 to reflect the Supreme Court decision in *Daubert.* The Rule provides as follows:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

Fed.R.Evid. 702. This rule requires a court to act as a "gatekeeper" to ensure that expert testimony is both relevant and reliable. *Pineda v. Ford Motor Co.,* 520 F.3d 237, 243 (3d Cir.2008). Rule 702 has a " 'liberal policy of admissibility.' " *Id*. (quoting *Kannankeril v. Terminix Int'l, Inc.,* 128 F.3d 802, 806 (3d Cir.1997)). The burden of showing expert testimony is admissible, once challenged, lies with the offering party. *See Kannankeril,* 128 F.3d at 807.

To be admissible, expert testimony must satisfy three requirements under Rule 702: 1) the witness must be an expert (i.e., must be qualified); 2) the expert must testify about matters requiring scientific, technical, or specialized knowledge (i.e., must be reliable); and 3) the expert's testimony must assist the trier of fact (i.e, must fit). *Id.* at 806 (citing *In re Paoli R.R. Yard PCB Litig. (Paoli II),* 35 F.3d 717, 742 (3d Cir.1994)); *Elcock v. Kmart Corp.,* 233 F.3d 734, 741 (3d Cir.2000) (stating three requirements are qualifications, reliability, and fit). An expert is qualified if

he " 'possesses specialized expertise.' " *Pineda,* 520 F.3d at 244 (quoting *Schneider ex rel. Estate of Schneider v. Fried,* 320 F.3d 396, 404 (3d Cir.2003)). The qualification requirement is liberally construed. *Id* .

A reliable opinion is "based on the 'methods and procedures of science' rather than on 'subjective belief or unsupported speculation'; the expert must have 'good grounds' for his or her belief." *Paoli II,* 35 F.3d at 742 (quoting *Daubert,* 509 U.S. at 589). The focus of the reliability inquiry is on the expert's principles and methodology, not on his conclusions. *Daubert,* 509 U.S. at 595. In determining reliability, a court may look to several non-exhaustive factors, including:

> (1) whether a method consists of a testable hypothesis; (2) whether the method has been subject to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique's operation; (5) whether the method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable; (7) the qualifications of the expert witness testifying based on the methodology; and (8) the non judicial uses to which the method has been put.

***5** *Elcock,* 233 F.3d at 745–46 (quoting *Paoli II,* 35 F.3d at 742 n. 8). Finally, an opinion fits a particular case (and thus helps the trier of fact) when there is a " 'connection between the scientific research or test result to be presented and particular disputed factual issues in the case.' " *Oddi v. Ford Motor Co.,* 234 F.3d 136, 145 (3d Cir.2000) (quoting *Paoli II,* 35 F.3d at 743). Fit is an issue of relevance and simply means that scientific validity of the method or principles applies to the issues at hand. *U.S. v. Ford,* 481 F.3d 215, 220 n. 6 (3d Cir.2007).

Target has not raised a proper *Daubert* challenge. Target does not challenge Dr. Gleimer's expertise, the reliability of his methodology, or the relevance of his opinion to this particular case. Target merely challenges the reliability of his conclusions. This is not the "inquiry envisioned by Rule 702." *Daubert v. Merrell Dow Pharmaceuticals, Inc.,* 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993). As the Supreme Court cautioned, the overarching subject of a challenge under Rule 702 is "the scientific validity and thus the evidentiary relevance and reliability—of the principles that underlie a proposed submission." *Id.* Consequently, the Court's focus "must be solely on principles and methodology, not on the conclusions that they generate." *Id.*

Even construing Target's motion as a challenge to the reliability of Dr. Gleimer's methodology, Target has not raised any justification for barring his opinions. Target first argues that Dr. Gleimer "elected to disregard the medical evidence" and failed to explain how Plaintiff's presentation to the emergency room could have been caused by her fall. Target Mot. Summ. J. at 30. Target also finds significant that Dr. Gleimer cannot state exactly how and when the knee dislocation occurred, but attributes the dislocation to "some event/injury while in the hospital." *Id.* Target further contends that Dr. Gleimer failed to explicitly state that his opinions are based upon a reasonable degree of medical probability or certainty. *Id.* at 31. However, Dr. Gleimer did explain at length his reasons for reaching this conclusion. *See* Dr. Gleimer Dep. at 42–45. The balance of Target's arguments may be properly raised on cross-examination, not on a Rule 702 challenge. Therefore, the Court will deny Target's request to bar Dr. Gleimer's opinions.

b. Negligence

In order to establish negligence under the laws of New Jersey, a plaintiff must establish: (1) a duty of care owed to Plaintiff, (2) a breach of that duty, (3) actual and proximate causation, and (4) damages. *Jersey Cent. Power & Light Co. v. Melcar Utility Co.,* 212 N.J. 576, 594 (2013). Target only challenges Plaintiffs' ability to establish the third prong—actual and proximate causation.

i. Proximate Causation

Target argues that Plaintiff cannot establish that Target's negligence was the proximate cause of her knee subluxation. Target accords little weight to Dr. Gleimer's opinion that an "event" occurred during her hospitalization, but argues that even accepting this conclusion, "it is not foreseeable [that] any treatment for this alleged injury would cause a stable, intact knee prosthetic to dislocate, even if that treatment

was negligently administered." Target's Mot. Summ. J. at 27. Target also highlights that Plaintiff's own expert "does not state [that] plaintiff was receiving treatment for her back when the knee dislocation occurred, or that the dislocation of plaintiff's was a foreseeable consequence of such treatment." *Id.* However, none of these arguments justify summary judgment.

***6** Under well-established principles of tort law, "a tortfeasor is generally held answerable for the injuries which result in the ordinary course of events from his negligence and it is generally sufficient if his negligent conduct was a substantial factor in bringing about the injuries." *Rappaport v. Nichols,* 31 N.J. 188, 156 A.2d 1, 9 (N.J.1959). Therefore, to be considered a proximate cause, "conduct need only be a cause which sets off a foreseeable sequence of consequences, unbroken by any superseding cause, and which is a substantial factor in producing the particular injury." *Bendar v. Rosen,* 247 N.J.Super. 219, 588 A.2d 1264, 1269 (N.J.Super.Ct.App.Div.1991) (quoting *Scafidi,* 574 A.2d at 398). The New Jersey Supreme Court has been clear that "[p]roximate cause is a factual issue, to be resolved by the jury after appropriate instruction by the trial court." *Scafidi v. Seiler,* 119 N.J. 93, 574 A.2d 398, 402 (N.J.1990).

Contrary to Target's arguments, Plaintiffs have identified a triable issue of fact as to causation. First, Plaintiffs have offered ample evidence that Plaintiff's visit to the emergency room was spurred by severe back and knee pain. In her deposition, Plaintiff states that she had her husband call an ambulance "because of the excruciating pain she was experiencing in her knee and back." Pls.' SDMF, ¶ 3. Dr. Gleimer opines, and some of the emergency records indicate, that Plaintiff presented to the hospital with complaints of severe left leg pain, back pain, and ambulatory pain. *Id.,* Ex. F; Ex. P–2 at 1. The records also note that Plaintiff complained of "pain to lower back" and that Plaintiff "ambulate[d] slowly without assistance." *Id.* at 6–7.

Although, as Plaintiff concedes, the reasons for her actual admission remain less certain, Plaintiffs have also produced sufficient evidence on this point to survive summary judgment. Plaintiffs' expert, Dr. Gleimer, concluded that there were multiple reasons for Plaintiff's admission and observed that she was treated almost exclusively for her low back pain and sciatica. Pls.' Opp'n at 5(citing Gleimer Dep. at 44–45). Dr. Gleimer notes that these painkillers can also suppress respiration. *Id.* Dr. Gleimer also highlights that Virtua's Admission Record lists back pain as "one of the conditions chiefly responsible for Ms. Geiss' admission to Virtua." *Id.* (citing Gleimer Dep. at 45–46). Dr. Lee, the admitting doctor on the date in question, also testified that Plaintiff was admitted, at least in part, for "low back pain." *Id.* (citing Lee Dep. at 29). Thus, Plaintiffs have produced adequate evidence for a jury to find that Target's initial negligence was a proximate cause of her knee subluxation.

ii. Actual Causation

Target also argues that Plaintiff's fall was not the actual cause of her knee subluxation. Essentially, Target argues that because an x-ray confirmed that Plaintiff's prosthetic knee was in place after her initial fall and because Dr. Gleimer cannot state with certainty how or when the knee dislocation occurred, Target cannot be the actual cause of her subsequent injury. This argument fundamentally misconstrues the meaning of "actual cause." Actual cause serves as an "important corollary to the proximate cause rule." *See Dawson v. Bunker Hill Plaza Associates,* 289 N.J.Super. 309, 326, 673 A.2d 847 (App.Div.1996). In order to impose liability, a plaintiff must also establish that defendant's negligent conduct was "a substantial factor in bringing about harm to another." *Id.* An actor's conduct is not a substantial factor, "if [the injury] would have been sustained even if the actor had not been negligent.' " *Id.*

***7** Taking the evidence in the light most favorable to the non-moving party, Plaintiffs have established that Target's conduct was an actual cause of the knee subluxation. Target incorrectly focuses on whether the fall was the direct cause of Plaintiff's injury. However, the law is clear that Target can be liable, "even where there are 'other intervening causes which were foreseeable or were normal incidents of the risk created.' " *Camp v. Jiffy Lube No. 114,* 309 N.J.Super. 305, 309–10, 706 A.2d 1193 (App.Div.1998). Target has not provided any valid basis for summary judgment. Therefore, Target's motion for summary judgment is DENIED.

B. Virtua's Motion for Summary Judgment

Virtua has also moved for summary judgment on Target's Third–Party Complaint against the hospital. Virtua argues that "[n]o party has factually established a prima facie claim against Virtua for negligence." Virtua Mot. Summ. J. at 5. Virtua also contends that to the extent that Target's claim against Virtua alleges medical malpractice, expert

testimony is required to establish a deviation from accepted medical standards. *Id.* at 4, 706 A.2d 1193. Target responds with a number of arguments, none of which are presented with particular lucidity. Target first argues that it need not produce expert testimony because the "common knowledge" exception applies. Target then contends that Virtua's negligent spoliation of evidence entitles Target to an adverse inference. Target also raises the doctrine of "unclean hands" to thwart Virtua's motion for summary judgment. Finally, Target attempts to assert a claim for fraudulent concealment. The Court will address these arguments in turn.

a. Negligence

It is axiomatic that "the mere showing of an incident causing the injury sued upon is not alone sufficient to authorize the finding of an incident of negligence." *Long v. Landy,* 35 N.J. 44, 54, 171 A.2d 1 (1961). As a third-party plaintiff, Target bears the burden of demonstrating the existence of negligence. *See Buckelew v. Grossbard,* 87 N.J. 512, 435 A.2d 1150, 1157 (N.J.1981) ("We start with the basic proposition that ordinarily negligence must be proved and will never be presumed, that indeed there is a presumption against it, and that the burden of proving negligence is on the plaintiff"). Negligence may only be inferred from proven facts and circumstances and cannot be based on speculation or conjecture. *Long,* 35 N.J. at 54, 171 A.2d 1.

Target largely ignores these well-settled principles and attempts to survive summary judgment without providing any competent evidence of Virtua's negligence. Target argues that "the 'event' presumably occurred as a result of the carelessness, negligence, and/or gross negligence of Virtua." Target's Opp'n at 9. However, the law is clear that negligence "will never be presumed." *Buckelew,* 435 A.2d at 1157. Target first attempts to surmount this obstacle by invoking the "common knowledge" exception. According to Target, the common knowledge exception is applicable "where a lay person using ordinary understanding and experience is sufficient to determine a defendant's negligence without the benefit of expert testimony." Target's Opp'n (citing *Bender v. Walgreen Eastern Co. ., Inc.,* 399 N.J.Super. 584, 590, 945 A.2d 120 (N.J.Super.Ct.App.Div.2008)). Target previously raised this same exception in its opposition to Virtua's prior motion to dismiss in relation to the Affidavit of Merit requirement. The Court rejected its application then and will do so again.[2] *See* Doc. No. 30 at 7. Moreover, even if the Court did apply the common knowledge exception, it would not obviate Target's obligation to establish negligence. It merely alters the proofs upon which a plaintiff may rely to demonstrate a deviation from the standard of care.

***8** In addition to raising the common knowledge exception, Target makes two ill-fated attempts to establish a duty by Virtua. Target Mot. Summ. J. at 11. Target appears to argue that Virtua breached some duty to Target by failing to preserve evidence, which prejudiced Target. However, Target has not identified the source of such a duty. To the extent that Target relies on a common law duty to preserve evidence, Target has not established any of the required elements. The duty to preserve evidence only arises when there is pending or likely litigation between two parties, knowledge of this fact by the alleged spoliator, evidence relevant to the litigation, and the foreseeability that the opposing party would be prejudiced by the disposal of this evidence. *Cockerline v. Menendez,* 411 N.J.Super. 596, 620, 988 A.2d 575 (App.Div.2010). Target also argues that Virtua violated a statutory duty, imposed by N.J. 13:35–6.5, by failing to maintain complete and accurate records.[3] However, the statute does not give rise to a cause of action. *See Proske v. St. Barnabas Med. Ctr.,* 313 N.J.Super. 311, 318–19, 712 A.2d 1207 (App.Div.1998) (finding that N.J.S.A. 26:8–5 does not create a statutory cause of action and that "violation of the statute did not have a causal relation to the physical injury suffered"). Therefore, Target has not alleged any fact, much less provided competent evidence, of Virtua's negligence.[4]

b. Fraudulent Concealment of Evidence

Target also asserts a claim for fraudulent concealment of evidence against Virtua.[5] In order to prove this tort, a plaintiff must demonstrate that: (1) the defendant in the fraudulent concealment action had a legal obligation to disclose evidence in connection with *existing* or *pending* litigation, (2) the evidence was material to the litigation, (3) the plaintiff could not have reasonably obtained the evidence elsewhere, (4) the defendant *intentionally* withheld, altered, or destroyed evidence with purpose to disrupt litigation, (5) Plaintiff was damaged by having to rely on an incomplete record that did not contain the evidence defendant concealed. (emphasis added) *Rosenblit v. Zimmerman,* 166 N.J. 391, 406–07, 766 A.2d 749 (2001). Target has not established these elements. Target has not provided any evidence that the missing records may have been material to this litigation. Target has not even established that Virtua intentionally

withheld the missing entries. Even under the favorable standard of review on summary judgment, Target's claims cannot survive.

In the Third–Party Complaint, Target alleged claims for negligence and what this Court will construe as fraudulent concealment of evidence against Virtua. However, Target has failed to "make a showing sufficient to establish the existence of an element essential to [its] case." *Celotex,* 477 U.S. at 322. Therefore, the Court will grant Virtua's motion for summary judgment. [6]

IV. CONCLUSION

For the foregoing reasons, Target's Motion for Partial Summary Judgment is DENIED. Virtua's motion for summary judgment is GRANTED. An appropriate order shall issue today.

ORDER

***9 THIS MATTER** having come before the Court on the motions of Virtua Memorial Hospital ("Virtua") and Target Corporation ("Target") for summary judgment, pursuant to Federal Rule of Civil Procedure 56, and the Court having considered the moving papers and attached documents, and the responses thereto, and for the reasons expressed in the Opinion issued this date;

IT IS HEREBY ORDERED that Target's motion for summary judgment is **DENIED.**

IT IS HEREBY FURTHER ORDERED that Virtua's motion for summary judgment on Target's Third Party Complaint is **GRANTED.**

All Citations

Not Reported in F.Supp.2d, 2013 WL 4675377

Footnotes

1 Plaintiff remained in the hospital until she was discharged on October 11, 2007. Target's SUMF, ¶ 24.

2 In the August 2, 2011 Opinion and Order, the Court stated: "Target has not demonstrated that its claim turns on common knowledge. Target alleges only that 'something' happened while Mrs. Geiss was at Virtua that caused her injuries. Target does not allege that an obvious error by Virtua or its employees caused Mrs. Geiss' injuries. Rather, Target acknowledges that it does not know the exact cause of her injuries. Because Mrs. Geiss received medical treatment, her injuries may have resulted from negligent medical care that requires expert testimony to prove."

3 Virtua notes that Target relies on the wrong statutory provision provision. According to Virtua, NJAC 13:35–6.5 is an administrative code and is not applicable to institutions. Virtua instead posits that NJSA 26:8–5 is the appropriate statutory provision mandating the maintenance of records.

4 Virtua also urges the Court to apply the doctrine of "unclean hands" and deny Virtua's motion for summary judgment. This doctrine "gives expression to the equitable principle that a court should not grant relief to one who is a wrongdoer with respect to the subject matter in the suit." *Faustin v. Lewis,* 85 N.J. 507, 427 A.2d 1105, 1107 (N.J.1981). As with every other argument in Target's opposition, Target has not demonstrated how this doctrine would be applicable. Although it is unfortunate that Virtua could not provide Plaintiff's complete medical record in discovery, Target has not provided any evidence of "wrongdoing with respect to the subject matter in the suit." Jennifer Raio testified that despite their best efforts in searching, her team had not been able to uncover the missing records. Jennifer Raio Dep., Target's Opp'n, Ex. D, 33–34. Moreover, Target has not produced any evidence or testimony linking Virtua's failure to maintain records to Plaintiff's actual injury.

5 The Third Party Complaint does not explicitly articulate a claim for fraudulent concealment, but it does contain allegations of spoliation of evidence. As Target states, spoliation of evidence claims are recognized as the tort of fraudulent concealment. *See* *Rosenblit v. Zimmerman,* 166 N.J. 391, 406, 766 A.2d 749 (2001).

6 Target also seeks an adverse inference jury instruction based on Virtua's alleged spoliation of evidence. Even if the Court were denying Virtua's motion, the Court would not be inclined to address jury instruction requests on a motion for summary judgment.

End of Document

Exhibit 14

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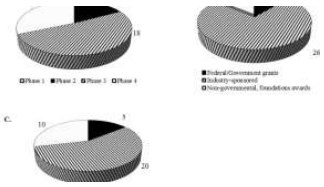

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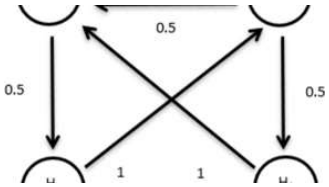

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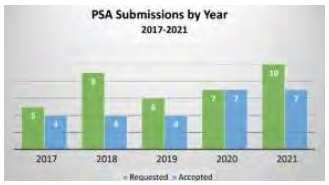

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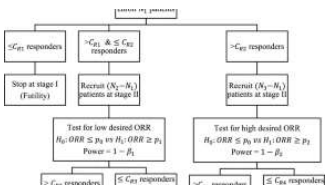

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ALS 463: Current Issues for FDA Regulated Products

Course Number: ALS 463
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Semester: Fall
No. Units: 3.0
Faculty/Instructor(s): Susan Bain (http://www.kgi.edu/x12768.xml)

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The business environment and regulatory framework pertaining to the medical products industry continue to change rapidly, as they are constantly challenged by competition, politics and new technological possibilities. The highly lucrative and competitive nature of this industry requires professionals have a good working knowledge, background and understanding of FDA's most recent developments, trends and legislation affecting product development, licensing and manufacturing of current and future pharmaceutical products and devices.

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ALS 462, Introduction to Food and Drug Law recommended but not required for successful completion of this course. Students who have not taken ALS 462 should purchase and review the textbook required for ALS 462: Fundamentals of US Regulatory Affairs, Seventh Edition.

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By the end of this course the students will have been exposed to and understand the background, requirements and challenges involved with new regulations, enforcement activities and product requirements facing the ever-changing landscape of the regulated medical products industry.

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The students will be able to analyze current practices and procedures used at pharmaceutical and medical device firms and make recommendations to management regarding emerging "best practices" in regulatory, quality and marketing, effecting product development, manufacturing and sale of finished drugs and devices.

Exhibit 16

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978-0-12-811155-0

Language

English

Published

2018

Imprint

Academic Press

DOI

https://doi.org/10.1016/C2016-0-00994-4

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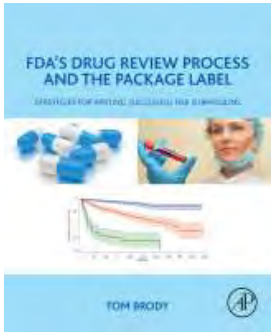

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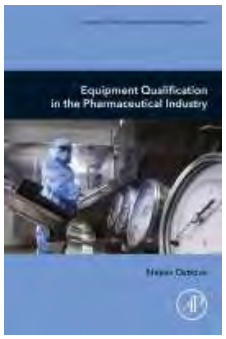

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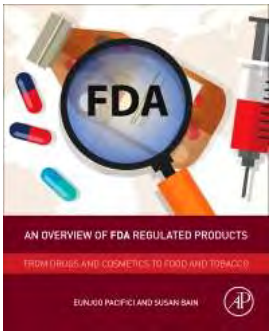

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Guidance for Industry

Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches

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This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact David Jacobson-Kram at 301-796-0175.

U.S. Department of Health and Human Services
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Guidance for Industry[1]
Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to inform pharmaceutical manufacturers of the Food and Drug Administration's (FDA's) current thinking regarding genotoxic and carcinogenic impurities in drug substances and drug products, including biologic products that are regulated by the Center for Drug Evaluation and Research (CDER). This guidance provides recommendations on how to evaluate the safety of these impurities during clinical development (investigational new drug applications (INDs)) and for marketing applications (new drug applications (NDAs), biologics license applications (BLAs), and abbreviated new drug applications (ANDAs)). This guidance provides recommended exposure thresholds on the clinical exposure to genotoxic or carcinogenic impurities. Also provided are additional testing and exposure threshold recommendations for situations where there are known or theoretical safety concerns based on available data, structural alerts, and/or assessment of the synthetic pathway.

This guidance is intended as an adjunct to the ICH guidances for industry *Q3A(R2) Impurities in New Drug Substances*, *Q3B(R2) Impurities in New Drug Products*, and *Q3C(R3) Impurities: Residual Solvents* that deal with the topic of impurities in a more general fashion.[2] This guidance provides specific recommendations regarding the safety qualification of impurities with known or suspected genotoxic or carcinogenic potential while the ICH guidances provide only general direction. This guidance addresses synthetic impurities and degradants in drug substances, but does not otherwise address the genotoxicity or carcinogenicity of actual drug substances or intended drug product ingredients. This guidance also applies to known starting materials or anticipated reaction products.

[1] This guidance has been prepared by the Office of New Drugs in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] See http://www.fda.gov/cder/guidance/index.htm. The FDA has incorporated revision 3 (R3) of ICH Q3C into the guidance for industry *Q3C — Tables and List*, which is posted on the CDER guidance Web site.

This guidance describes a variety of ways to characterize and reduce the potential lifetime cancer risk associated with patient exposure to genotoxic and carcinogenic impurities both during clinical development and after approval. These approaches include:

- Changing the synthetic and/or purification routes to minimize the formation and/or maximize the removal of the relevant impurity.

- Allowing a maximum daily exposure target of 1.5 µg per day for the relevant impurity as a general target for marketed products, though higher levels may be acceptable during clinical development. Certain impurities with structural alerts suggesting particularly high genotoxic and carcinogenic potential would not be appropriate for this general threshold approach and would need to be evaluated on a case-by-case basis.

- Further characterizing the genotoxic and carcinogenic risk via mechanism of action or weight-of-evidence approaches, or through additional studies to better support appropriate impurity specifications.

This guidance also applies to drug products approved before the issuance of this guidance, but only in the presence of a specific safety signal that suggests the potential for an increased carcinogenic risk associated with the presence of an impurity or degradant, or with regard to a supplemental application for a previously approved drug product that proposes a significant change in the drug product's approved labeling that suggests the potential for an increased carcinogenic risk associated with the presence of an impurity or degradant (e.g., new indication, new dosage regimen, longer duration of use). Applicants also should take these recommendations into consideration when preparing supplemental manufacturing submissions to NDAs, BLAs, and ANDAs, such as submissions proposing new formulations or new synthetic routes. Although this guidance applies to impurities present in biologic products regulated by CDER, it is noted that, in most cases, the genotoxicity assays conducted for small molecule pharmaceuticals are not applicable to biopharmaceuticals. Likewise, the standard assessment of the genotoxic potential of impurities in biopharmaceuticals may not be appropriate in many cases since they may include residual host cell proteins and nucleic material, fermentation components, and bacterial and viral components and do not include organic chemicals typically found in small molecule manufacturing.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Compounds that have been demonstrated to induce genetic mutations, chromosomal breaks, and/or chromosomal rearrangements are considered genotoxic and have the potential to cause

cancer in humans. Exposures to even low levels of these impurities may be of significant concern. Therefore, the identification limits provided in ICH Q3A(R2) and ICH Q3B(R2) may not be acceptable for genotoxic or carcinogenic impurities. For instance, under some scenarios the limits in these ICH guidances would allow a genotoxic or carcinogenic impurity to be present in a drug product at a level resulting in exposures up to 3,000 µg per day without needing identification. Although genotoxic and carcinogenic properties can be acceptable for some active pharmaceutical ingredients (APIs) depending on clinical circumstances (e.g., cancer chemotherapies), impurities in drug substances and drug products generally do not have beneficial effects and may impose a risk without associated benefit. Therefore, manufacturers should strive to achieve the lowest levels of genotoxic or carcinogenic impurities that are technically feasible and/or levels that convey no significant cancer risk.

Currently available guidances that address issues related to impurities and residual solvents include ICH Q3A(R2), ICH Q3B(R2), and ICH Q3C(R3). In addition, the European Medicines Agency's (EMEA) Committee for Medicinal Products for Human Use (CHMP) published a guideline regarding limits of genotoxic impurities.[3] These documents are discussed below to provide a background to this guidance, but the inclusion of the EMEA guideline in this background discussion should not be interpreted as an FDA endorsement of that document.

A. ICH Guidances for Industry Relating to Drug Impurities and Residual Solvents

ICH Q3A(R2) and ICH Q3B(R2) address the issue of impurities in drug substances and drug products, respectively. ICH Q3A(R2) addresses the identification and qualification of impurities in drug substances approved after the issuance of the guidance, and ICH Q3B(R2) addresses only those impurities in drug products approved after the issuance of the guidance that are classified as degradation products of the drug substance or reaction products of the drug substance with an excipient and/or immediate container closure system. These guidances define an impurity as any component of the drug substance or drug product other than the chemical entity that makes up the drug substance or an excipient in the drug product. Depending on the quantity of drug substance or drug product to which a patient is exposed, these guidances recommend thresholds for the identification, reporting, and qualification of impurities. *Qualification*, as defined by the two guidances, is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity (or degradation product) or a given impurity (or degradation) profile at the level(s) specified.[4] Higher or lower thresholds for qualification can be considered appropriate based on scientific rationale and level of concern.[5]

These guidances recommend when, after consideration of factors such as the patient population and duration of use, qualification studies of an impurity are appropriate. Part of the battery of tests used to qualify an impurity could include assays to determine whether the impurity is

[3] Guideline on the Limits of Genotoxic Impurities (EMEA guideline), June 2006 (http://www.emea.europa.eu).

[4] See the Glossary sections in ICH Q3A(R2) and ICH Q3B(R2).

[5] See ICH Q3A(R2), section VII, and ICH Q3B(R2), section VI.

genotoxic.[6] These guidances also recommend that, when considered appropriate, assays to assess genotoxic potential include the "minimum screen" of in vitro assays: a gene mutation assay and a chromosomal aberration assay.[7] ICH Q3A(R2) indicates that "such studies can be conducted on the new drug substance containing the impurities to be controlled, although studies using isolated impurities can sometimes be appropriate."[8] A similar recommendation is included in ICH Q3B(R2).

It should be noted, however, that allowing genotoxicity assessment of the impurity as it is present with the drug substance, rather than in isolation, renders the genotoxicity assessments much less sensitive. For example, the potent mutagens that are typically used as positive controls in the bacterial mutation assay, such as 9-aminoanthracene and methyl methanesulfonate, when present with a noncytotoxic drug substance at the minimal level for qualification, would not be detected by these genotoxicity assays because the maximum concentration of the impurity at the limit concentration of the drug substance would not be sufficient to produce a genotoxic response in the assays. If the drug substance is cytotoxic, this approach of assessing the impurity as it is present with the drug substance would be even more insensitive, since the drug's toxicity would further limit the level at which the impurity could be tested.

Although the ICH guidances provide some recommendations on the types of tests that should be conducted, the guidances do not provide specific recommendations on how to proceed if one or both of the genetic toxicology tests are positive; they simply state that additional testing, removal of the impurity, or lowering the level of the impurity should be considered.

ICH Q3C(R3) recommends acceptable concentration limits or permissible daily exposures for various classes of solvents, which are one type of impurity. The guidance does not, however, include a recommendation on limiting exposure based upon concerns for genotoxic potential. The guidance recommends only that mathematical models be used for setting exposure limits in cases where reliable carcinogenicity data are available.

The ICH guidances on impurities and residual solvents do not apply to drug substances or drug products used during the clinical research stages of development.

B. EMEA Proposed Guideline on Limits of Genotoxic Impurities

In June 2006, the EMEA's CHMP published a guideline on the limits of genotoxic impurities in support of a marketing application.[9] A subsequent CHMP safety working party published a

[6] See ICH Q3A(R2), section VII and Attachment 3, and ICH Q3B(R2), section VI and Attachment 3.

[7] Ibid.

[8] See ICH Q3A(R2), section VII.

[9] EMEA guideline (http://www.emea.europa.eu)

question and answers document to provide clarification on the 2006 guideline.[10] This guideline recommends dichotomizing genotoxic impurities into those for which there is "sufficient (experimental) evidence for a threshold-related mechanism" and those "without sufficient (experimental) evidence for a threshold-related mechanism." The genotoxic impurities with sufficient evidence for a threshold-related mechanism would be addressed using methods outlined in ICH Q3C(R3) for Class 2 solvents. This approach calculates a "permitted daily exposure," which is derived using the "no observed effect level" or, alternatively, the "lowest observed effect level" from the most relevant animal study and incorporating a variety of uncertainty factors. Examples of genotoxic compounds that might fall into this category include compounds that induce aneuploidy by interfering with the mitotic spindle, compounds that interfere with the activity of topoisomerase, and/or compounds that inhibit DNA synthesis.

For genotoxic impurities without sufficient evidence for a threshold-related mechanism, the guideline proposes a policy of controlling levels to "as low as reasonably practicable" (called the *ALARP principle*). The ALARP approach specifies that every effort should be made to prevent the formation of such impurities during drug substance synthesis and, if that is not possible, technical effort should be made post-synthesis to reduce impurities (e.g., purification steps). Compounds that fall into this category are those that interact with DNA either directly or indirectly, such as alkylating agents, intercalating agents, or agents that can generate free radicals. Since any exposure to these agents can convey some level of carcinogenic risk, and since complete elimination of genotoxic impurities from drug substances is often unachievable, the presence of a concerning impurity requires the implementation of a concept of an acceptable risk level. Methods for the derivation of acceptable risk levels are discussed in ICH Q3C(R3), Appendix 3, in reference to Class 1 carcinogenic solvents.

Although the approach described above is acceptable, in most instances mechanistic data sufficient to allow for an assessment of whether there is a threshold mechanism are lacking. Furthermore, it is relatively uncommon for there to be sufficient data to allow for a quantitative risk assessment. The EMEA guideline recognizes these limitations and, therefore, proposes the use of a "threshold of toxicological concern" (TTC) for genotoxic impurities. The TTC refers to a threshold exposure level to compounds that does not pose a significant risk for carcinogenicity or other toxic effects. The EMEA guideline recommends a TTC of 1.5 µg per day for all but a highly potent subset of compounds. This threshold corresponds to an incremental 10^{-5} lifetime risk of cancer, a risk level that the EMEA considers justified because of the benefits derived from pharmaceuticals. The guideline indicates that a TTC value higher than 1.5 µg per day may be acceptable based on a weight-of-evidence approach to the profile of genotoxicity results, in situations where the anticipated human exposure will be short-term, for the treatment of life-threatening conditions, when life expectancy is less than 5 years, or where the impurity is a known substance and human exposure will be much greater from other sources. The derivation of the TTC is discussed in more detail in section IV.B.1.

The approach taken in the EMEA guideline for setting an exposure limit for genotoxic or carcinogenic impurities in drug products in support of a marketing application is reasonable. However, issues regarding the presence of genotoxic or carcinogenic impurities often occur

[10] Question & Answers on the CHMP Guideline on the Limits of Genotoxic Impurities, June 2008 (http://www.emea.europa.eu)

during the clinical development stages. Therefore, this guidance provides recommendations for acceptable exposure thresholds during clinical development as well as for marketing applications.

III. RECOMMENDED APPROACHES FOR INITIAL ASSESSMENT OF GENOTOXIC POTENTIAL OF IMPURITIES

If adequate data characterizing genotoxic and carcinogenic potential are not already available, impurities identified in drug substances or drug products at levels exceeding the stated qualification thresholds in the relevant ICH guidances should be assessed for genotoxic potential in an initial minimal screen. Assays conducted with the impurity in isolation are recommended. However, studies with the drug substance containing, or spiked with, the impurity can be considered in cases where it can be demonstrated that synthesizing sufficient amounts of the impurity is infeasible.

As mentioned, the ICH guidances on impurities do not apply to drug substances or drug products for use in clinical trials. However, in cases where the presence of an impurity with genotoxic or carcinogenic potential is identified or where such an impurity may be expected based on the synthetic pathway, steps should be taken during the clinical development stage to address safety concerns associated with these impurities.

If an impurity that is present at levels below the ICH qualification thresholds is identified, the impurity should be evaluated for genotoxicity and carcinogenicity based on structural activity relationship (SAR) assessments (i.e., whether there is a *structural alert*). This evaluation can be conducted via a review of the available literature or through a computational toxicology assessment; commonly used software includes MDL-QSAR, MC4PC, and Derek for Windows. The conduct of an in vitro mutation assay (i.e., bacterial reverse mutation assay) generally would be an acceptable initial screen for impurities with an identified alert, since positive signals in computational toxicology programs are often derived from the results of bacterial mutation assays and mutagenic carcinogens are considered to operate through nonthreshold-related mechanisms. An assessment in a mammalian cell assay may be needed for impurities with specific structural groups, such as carbamates, that are not well characterized in bacterial assays, or for compounds that are toxic to *E. coli* and *Salmonella*, such as antibiotics.

If the initial evaluation of the genotoxic potential of an impurity is negative, no further genotoxicity studies are recommended and the impurity should be considered to be adequately qualified regarding its genotoxic potential. It should be noted that in cases where it is necessary from a feasibility standpoint to conduct the assays with the drug substance containing, or spiked with, the impurity, the proposed acceptance criterion should be commensurate with the level of impurity observed in clinical, stability, and/or production batches, taking into consideration the manufacturing and analytical variability. This acceptance criterion should not exceed the level present in the drug batch used in the genotoxicity assay and should be supported by the relevant qualification thresholds discussed in the ICH guidances or supporting general toxicity information.

In some cases, the structure of an impurity leading to the structural alert is shared with the API. The genotoxic potential of such an impurity can be evaluated through the standard testing of the API if the chemical environment for the alerting structure of the compounds is deemed comparable for the reactivity potential.

IV. RECOMMENDED APPROACHES FOR HANDLING GENOTOXIC AND CARCINOGENIC IMPURITIES

Positive results in one or more genotoxicity assays or other information indicating a carcinogenic potential, such as positive data from a carcinogenicity study with the impurity, should be addressed further. Recommended approaches for handling genotoxic or carcinogenic impurities are described in this section and are summarized in Table 2 at the end of section IV.C. A decision tree is also included in Appendix A.

A. Prevention of Genotoxic and Carcinogenic Impurity Formation

Since drug-related impurities presumably provide limited, if any, therapeutic benefits and because of their potential to cause cancer in humans, every feasible technical effort should be made to prevent the formation of genotoxic or carcinogenic compounds during drug substance synthesis or drug product manufacturing. However, we recognize that completely preventing the formation of or removing an impurity of concern may not be possible in many cases.

B. Reduction of Genotoxic and Carcinogenic Impurity Levels

In lieu of completely preventing the formation of a genotoxic or carcinogenic impurity, steps to reduce the level of impurity present in the drug substance or drug product should be considered. The following sections discuss acceptable thresholds to support safety during clinical development and for a marketing application. Analytical methodologies should be used that can adequately identify impurities of concern at levels associated with the relevant qualification thresholds. This threshold approach should be applied only in the absence of adequate qualification data (data that establish the biological safety of an impurity at the level specified) for the given impurity.

1. Acceptable Levels to Support Marketing Applications

In general, an exposure level of 1.5 µg per person per day for each impurity can be considered an acceptable qualification threshold for supporting a marketing application. Any impurity found at a level below this threshold generally should not need further safety qualification for genotoxicity and carcinogenicity concerns. The threshold is an estimate of daily exposure expected to result in an upper bound lifetime risk of cancer of less than 10^{-6} (one in a million), a risk level that is thought to pose negligible safety concerns. The threshold was based on an analysis of the carcinogenic potencies of 477 chemicals and was derived from the probability distribution of carcinogenic potencies of those compounds.[11] Subsequent analyses of an

[11] Fiori, JM and RD Meyerhoff, 2002, Extending the Threshold of Regulation Concept: De Minimis Limits for Carcinogens and Mutagens, Reg Toxicol Pharmacol, 35, 209-216.

expanded carcinogenic potency database of more than 700 carcinogens further confirmed the threshold.[12] An additional analysis of subsets of highly potent carcinogens suggested that a threshold of 0.15 µg per day, corresponding to a 10^{-6} lifetime risk of cancer, may be more appropriate for chemicals with structural alerts for potential genotoxicity.[13] However, there are some compounds containing certain structural groups (aflatoxin-like-, N-nitroso-, and azoxy-structures) that have extremely high carcinogenic potency and are excluded from the threshold approach.

Federal regulatory agencies in the United States, such as the Environmental Protection Agency (EPA) (in the context of ambient water quality criteria), typically use a 10^{-6} lifetime risk of cancer to determine *negligible* risk from chemical exposures.[14] This approach supports an acceptable threshold level for genotoxic or carcinogenic impurities of 0.15 µg per day. However, other regulatory bodies have proposed a 10^{-5} level as an acceptable cancer risk.[15,16] Given that there is an overriding expected benefit of an approved drug product, a daily exposure level of 1.5 µg per day, associated with a 10^{-5} lifetime risk of cancer, can be acceptable for most genotoxic or carcinogenic impurities for a marketing application. This level of exposure is expected to produce a negligible increase in carcinogenic risk based on the existing background rate of human cancer and the conservative nature of cancer risk assessments. Additionally, this threshold is considered to be low enough to ensure that the presence of a compound with an uncharacterized genotoxic or carcinogenic potential would not significantly alter the risk-benefit ratio of a drug product, even if the impurity is later shown to be a carcinogen.

The database from which the exposure threshold for genotoxic or carcinogenic impurities is derived includes studies that primarily use oral administration, though a smaller number use the inhalation route. Although the recommended threshold approach applies to all drug products regardless of the intended route of administration, the qualification threshold of 1.5 µg per day may not be appropriate for some routes (e.g., dermal, ophthalmic) because of the lack of a relevant database from which an exposure threshold can be derived. Applicants should contact specific drug review divisions regarding acceptable approaches in these cases.

As part of this threshold approach, applicants can conduct and provide to the FDA an SAR assessment to identify structural similarities to known carcinogens. In cases where significant structural similarities to a known carcinogen are identified, an estimate of the potential human

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[12] Ibid.

[13] Kroes, R, AG Renwick, M Cheeseman, J Kleiner, I Mangelsdorf, A Piersma, B Schilter, J Schlatter, F Schothorst, JG Vos, and G Würtzen, 2004, Structure-Based Threshold of Toxicological Concern (TTC): Guidance for Application to Substances Present at Low Levels in the Diet, Food Chem Toxicol, 42, 65-83.

[14] U.S. Environmental Protection Agency, Office of Water and Office of Science and Technology, 2000, Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health, document number EPA-822-B-00-004, section 1.5.3 (http://www.epa.gov/waterscience/humanhealth/method/complete.pdf).

[15] See EMEA guideline, section 5.2.3.

[16] World Health Organization Guidelines for Drinking-Water Quality, 2nd ed., Vol. 2, 1996, Health Criteria and Other Supporting Information, Geneva, World Health Organization, section 12.4.2 (http://www.who.int/water_sanitation_health/dwq/gdwq2v1/en/index1.html).

cancer risk can be calculated based on the available information for the confirmed carcinogen. This assessment can result in an increase in the acceptable exposure threshold for impurities that are highly similar to carcinogens with relatively low potency, or a reduction in the limit for impurities that are highly similar to relatively potent carcinogens.

The EPA guidance *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (EPA/630/R-03/003F) regarding cancer susceptibility in pediatric populations indicates that children exposed to mutagenic carcinogens between age 0 (birth) and 16 have an increased cancer risk over a 70-year lifetime when compared to adults.[17] EPA concludes that cancer risks generally are higher from early-life exposure than from similar exposure durations later in life and recommends the application of adjustment factors to risk calculations to account for this observation. EPA recommends an adjustment factor of 10 for exposures before 2 years of age (i.e., spanning a 2-year time interval from the first day after birth up until a child's second birthday), which represents an approximation of the weighted geometric mean tumor incidence ratio from juvenile or adult exposures in repeated dosing studies. In the absence of data to calculate a specific dose-response adjustment factor for exposures between 2 and less than 16 years of age, EPA recommends an adjustment factor of 3, which represents an intermediate level of adjustment and reflects a midpoint between the 10-fold adjustment for the first two years of life and no adjustment (i.e., 1-fold) for adult exposures. However, the EPA guidance acknowledges that the resultant increases in cancer risk are relatively small for exposures that continue with fair uniformity over a lifetime. We recommend that this increase in susceptibility to carcinogens in pediatric populations be considered when determining the acceptable impurity level for a given drug product.

The threshold approach for genotoxic or carcinogenic impurities limits the likelihood that any individual impurity in a given drug product will present more than a 10^{-5} excess cancer risk, but the approach is not intended to ensure an aggregate excess cancer risk of less than 10^{-5}. This means the threshold approach to individual impurities is not intended to limit the overall excess cancer risk to 10^{-5} from all impurities in a single drug product or from multiple drug products concomitantly administered. As discussed above, this approach is consistent with approaches taken by various regulatory bodies such as EPA, World Health Organization, and EMEA in implementing threshold levels for carcinogenic risk when no benefit from the expected exposure is perceived. However, in cases where a class or family of structurally similar impurities is identified and is expected to have similar mechanisms resulting in their genotoxic or carcinogenic potential, the total daily exposure to the related compounds should be evaluated relative to the recommended threshold exposure.

We recognize that drug products are often indicated for short-term use. However, for most drugs, these threshold considerations still apply since a drug may be used multiple times by the same individual or may be used outside of its approved indication. A detailed rationale should be provided to the FDA to support limits higher than generally considered appropriate for a marketing application.

[17] See http://cfpub.epa.gov/ncea/index.cfm.

2. Acceptable Levels during Clinical Development

The previous section describes the qualification threshold for genotoxic or carcinogenic impurities in support of a marketing application. Issues related to genotoxic impurities also can arise during a drug product's clinical development period and can affect the assessment of safety for conducting the program. Some flexibility in the previously described threshold level can be applied during the investigational stages, since clinical trials vary widely in duration from short-term (single dose to 4 weeks) to years and the qualification threshold for a marketing application is based on lifetime risk estimates. On the other hand, it should be recognized that during early clinical development, a benefit of the drug cannot be assumed. We recognize that the ability to identify and control drug-related impurities during early developmental stages is limited because of issues related to scale and maturity of production processes. Taking all these considerations into account, higher daily levels of exposure to potentially genotoxic impurities may be acceptable during the clinical development of the drug product compared to what is appropriate for a marketed drug product.

Bos et al. reviewed the derived cancer risk from short-term, high-dose exposure to a genotoxic carcinogen relative to the same cumulative dose distributed over a lifetime (virtually safe dose).[18] Briefly, the authors state that only a limited number of animal studies have assessed the comparative tumor incidence from short-term versus long-term exposures with similar cumulative doses. From those studies that do exist, dose rate correction factors (factors by which a specific dose of a chemical carcinogen at long-term, low-dose rates should be multiplied to derive the expected tumor incidence from short-term, high-dose rates) ranged from unity to 8.3. The authors conclude that the most pragmatic approach to calculate acceptable short-term exposures to known genotoxic carcinogens is to linearly extrapolate the short-term exposure from the acceptable lifetime exposure or virtually safe dose.

Acceptable daily intakes of genotoxic impurities during clinical development are presented in Table 1, based on the linear extrapolation approach described by Bos et al. The impurity threshold exposures for exposure durations of up to 12 months are based on a 10^{-6} cancer risk level (0.15 µg per day for a lifetime exposure), since these trials often include healthy subjects for whom there is no expected health benefit and the efficacy of the drug may still be uncertain. The values are derived from a linear extrapolation from the qualification threshold using the maximum duration of dosing for each time period specified in Table 1. In addition, these values incorporate an uncertainty factor of 2 to allow for deviations from the linear extrapolation model. For trials greater than 1-year duration, the threshold value is identical to the threshold for a marketing application and is based on a 10^{-5} cancer risk level (1.5 µg per day derived from lifetime exposures); subjects in these trials generally have the condition or disease being studied and are more certain to derive benefit from the treatment than subjects in early trials. When determining the acceptable impurity threshold exposure, the specifics of the patient population in the clinical trial should be evaluated.

[18] Bos, PMJ, B Baars, TM Marcel, and MTM van Raaij, 2004, Risk Assessment of Peak Exposure to Genotoxic Carcinogens: A Pragmatic Approach, Toxicol Letters, 151:43-50.

Table 1: Acceptable Qualification Thresholds for Genotoxic and Carcinogenic Impurities

	Duration of Clinical Trial Exposure					
	< 14 days	**14 days to 1 mo**	**1 mo to 3 mos**	**3 mos to 6 mos**	**6 mos to 12 mos**	**> 12 mos**
Genotoxic and carcinogenic impurity threshold (µg/day)	120	60	20	10	5	1.5

C. Additional Characterization of Genotoxic and Carcinogenic Risk

In cases where attempts to prevent the formation of an impurity of concern and/or to reduce the amount of the impurity to an acceptable level as per Table 1 are not possible, further characterization of the genotoxic and carcinogenic potential should be conducted. The guidance for industry and review staff *Recommended Approaches to Integration of Genetic Toxicology Study Results* describes the FDA's current thinking regarding appropriate additional evaluations that can be conducted.[19] Briefly, these concepts include the consideration of the mechanism of action, weight of evidence, or the conduct of additional supportive studies. These concepts also can be considered relevant for genotoxic impurities.

In addition to the above considerations, the conduct of an SAR evaluation of an impurity may provide useful information. When a significant structural similarity to a known carcinogen is identified, the drug substance and drug product acceptance criteria (typically in units of parts per million or percent) can be set at a level that is commensurate with the risk assessment specific to that of the known compound. As noted previously, the proposed factors should be considered in light of manufacturing batch data.

Table 2 summarizes the recommended approaches for characterizing the presence and addressing the safety of genotoxic and carcinogenic impurities depending on the clinical development stage.

[19] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

Table 2: Recommended Approaches Based on Development Stage

Clinical Development Stage	Recommended Approach
IND	• Evaluate identified impurities for genotoxic and carcinogenic risk via SAR assessment • Conduct assay for the presence of anticipated genotoxic and carcinogenic impurities • If impurity with genotoxic and carcinogenic potential is identified: – Modify synthetic pathway to eliminate the impurity, if possible OR – Conduct genotoxicity assays to characterize the genotoxic potential if not already known AND/OR – Set specification to that associated with a potential daily impurity exposure supported by compound-specific risk assessment or relevant qualification threshold (see Table 1)
Marketing application (NDA, BLA, or ANDA)	• Evaluate identified impurities for genotoxic and carcinogenic risk via SAR assessment • If impurity with genotoxic and carcinogenic potential is identified: – Conduct genotoxicity assays to characterize the genotoxic potential if not already known AND/OR – Set specification to that associated with a potential daily impurity exposure supported by compound-specific risk assessment or 1.5 µg per day threshold

D. Considerations for Flexibility in Approach

The previous sections are intended to be general recommendations to consider when developing a drug product in which a potentially genotoxic or carcinogenic impurity is identified. We recognize that these approaches may not necessarily apply to every development program, and flexibility in the application of these recommendations may be appropriate. When applying the recommendations, consideration should be given to the drug product's clinical development stage, the maximum duration of drug administration at that stage, the proposed indication (e.g., treatment of a life-threatening condition versus a less serious condition), the patient population (e.g., adults versus children), and the structural similarity of an impurity to a compound of known carcinogenic potency. In some of these cases, acceptance criteria higher than the recommended thresholds can be supported in the presence of a potential pharmacological benefit to patients. In rare cases, such as in the presence of highly potent carcinogens, decreases in the threshold also may be warranted. The appropriateness of a flexible approach should be informed by the feasibility of controlling impurity levels and the capabilities of the current process.

458 **APPENDIX A: DECISION TREE FLOW DIAGRAM**

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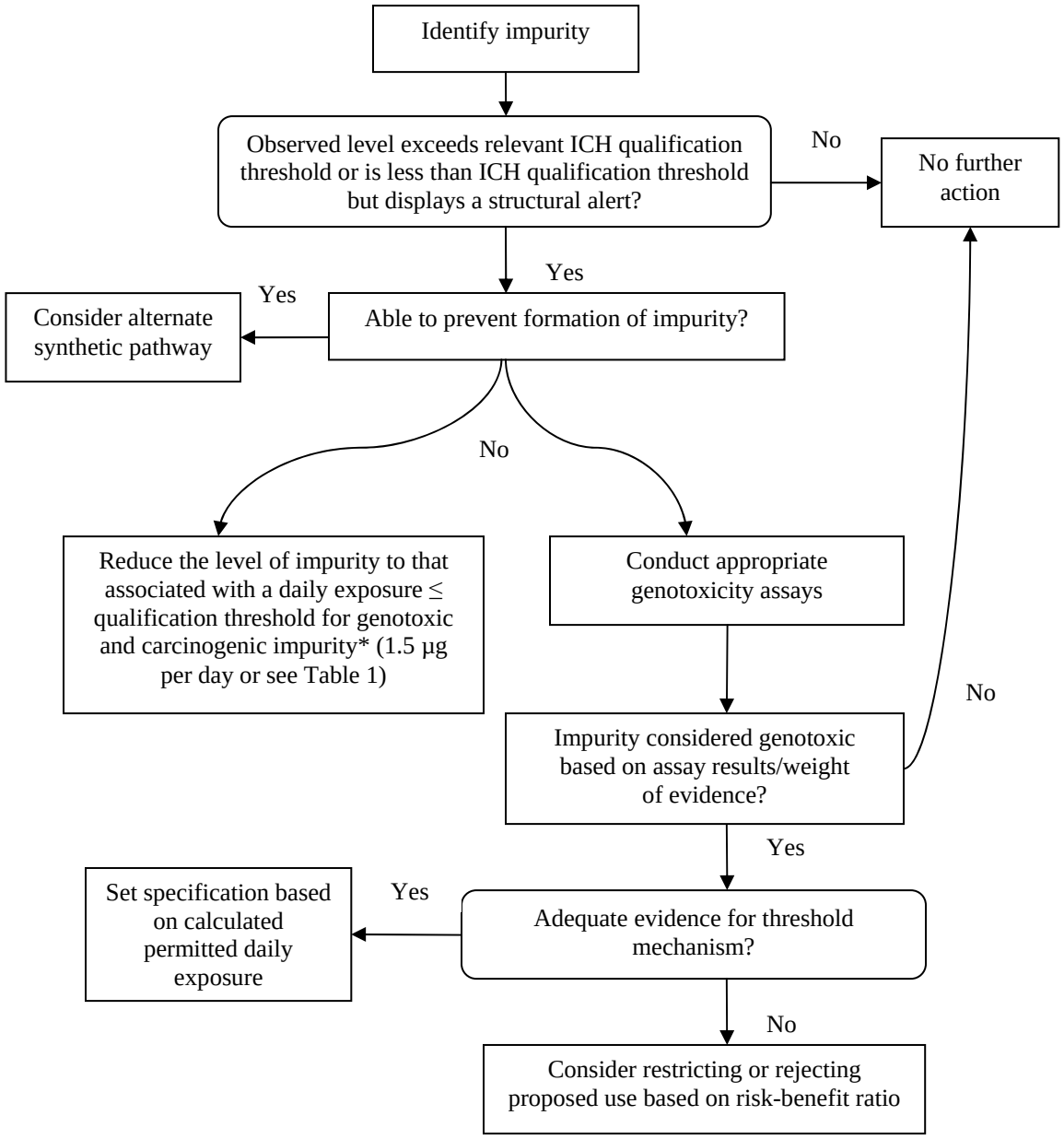

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*Safety threshold approach for genotoxic and carcinogenic impurities is not applicable to compounds with adequate data to derive compound-specific risk assessment or for those with SARs to high potency carcinogens. In addition, the approach may not be appropriate for some routes of administration (e.g., dermal, ophthalmic) because of the lack of a relevant database from which a threshold limit can be derived.

Exhibit 22

CHAPTER 56 – DRUG QUALITY ASSURANCE

SUBJECT:	IMPLEMENTATION DATE
ACTIVE PHARMACEUTICAL INGREDIENT (API) PROCESS INSPECTION Revision Note: Program revised 09/11/2015 to update implementation date, completion date, organizational/procedural changes and program contacts.	September 11, 2015 COMPLETION DATE

DATA REPORTING	
PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
Industry codes 54, 56 and 60-66 inclusive	Domestic / Foreign Inspections: 56002F (Full Inspection) 56002L (Abbreviated Inspection) Related PACs 56002 & H – Drug Process Inspections (DPI) 56002C & K – DPI / Radioactive Drugs 56002M – DPI/Therapeutic Biological Product Inspections

FIELD REPORTING REQUIREMENTS

Establishment Inspection Reports (EIRs) are to be created and filed electronically using the API specific module in TurboEIR or replacement system that is accessible to both ORA and CDER.

For inspections of routine commercial manufacturing classified as Official Action Indicated (OAI) due to deficiencies in Current Good Manufacturing Practice (CGMP) as they apply to APIs, submit advisory, administrative, or judicial action recommendations via MARCS-CMS in accordance with the Regulatory Procedures Manual (RPM).

Districts should immediately report significant issues according to current FACTS, Panorama and CMS procedures. This includes promptly filing and changing OAI notifications.

During an inspection, if you obtain information pertaining to inadequate adverse drug experience (ADE) reporting, unapproved drug issues, or post-approval reporting violations (application supplements, Field Alert Reports (FARs), etc.), report in accordance with directions provided in the applicable compliance programs and under separate captions in the EIR. Data system information about these inspectional activities should be reported under separate Program Assignment Codes (PACs). Expansion of coverage under these programs into a CGMP inspection should be reported under this compliance program.

This program provides guidance in evaluating compliance with CGMP and providing comprehensive regulatory coverage of all aspects of production and distribution of active pharmaceuticals ingredients (APIs) to assure that such products comply with Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act). As soon as the District becomes aware of any significant inspectional, analytical, or other information developed under this program that may affect the agency's new drug and abbreviated new drug approval decisions with respect to a firm, the District should report the information immediately according to current FACTS and EES procedures. This includes promptly filing and deleting OAI notifications.

Districts are to use this revised compliance program for CGMP inspections of API facilities.

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PART I - BACKGROUND

GENERAL

APIs are subject to the adulteration provisions of Section 501(a)(2)(B) of the Act, which requires all drugs to be manufactured in conformance with CGMP. No distinction is made between an API and a finished pharmaceutical in the Act and the failure of either to comply with CGMP constitutes a violation of the Act. FDA has not promulgated CGMP regulations specifically for APIs or drug components (as we have for finished pharmaceuticals). Thus, the use of "CGMP" in this document refers to the requirements of the Act rather than the requirements of 21 CFR Parts 210 and 211 regulations for finished pharmaceuticals.

FDA has long recognized that the CGMP requirements in the good manufacturing practice regulations for finished pharmaceuticals (21 CFR Parts 210 and 211) are valid and applicable in concept to active pharmaceutical ingredient (API) manufacturing. These concepts include, among others, building quality into the drug by using suitable equipment and employing appropriately qualified and trained personnel, establishing adequate written procedures and controls designed to assure manufacturing processes and controls are valid, establishing a system of in-process material and final drug tests, and ensuring stability of drugs for their intended period of use. In 2001, FDA adopted an internationally harmonized guidance to industry on API CGMPs in conjunction with regulatory partners in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This guidance is ICH Q7, *Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*. ICH Q7 represents the Food and Drug Administration's (FDA's) current thinking on CGMPs for API's. Thus, API and related manufacturing and testing facilities that follow this guidance generally will be considered to comply with the statutory CGMP requirement. However, alternate approaches may be used if such approaches satisfy the requirements of Section 501(a)(2)(B) of the Act as long as the approach ensure that the API meets its purported or represented purity, identity, and quality characteristics.

The term "active pharmaceutical ingredient" (API) is used in this program consistent with the meaning of this term as defined in ICH Q7. An active pharmaceutical ingredient is defined in ICH Q7 as "any substance or mixture of substances intended to be used in the manufacture of a drug product and that, when used in the production of a drug, becomes an active ingredient in the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body." Currently, other terms are also used by FDA and industry to mean an API. "Drug substance" and "bulk pharmaceutical chemical" (BPC) are terms commonly used to mean API and, for BPC, inactive ingredients. The use of these terms to describe active ingredients may be considered equivalent to the term used here, API.

FDA expects API manufacturers to apply CGMPs to the API process beginning with the use of starting materials, and to validate critical process steps that impact the quality and purity of the final API. Controls over material quality are expected to increase as the process approaches the final API. The level of control needed is highly dependent on the manufacturing process and increases throughout the process as it proceeds from early intermediate steps to final isolation

and purification steps. The appropriate level of control depends on the risk or criticality associated with each specific process step.

ICH Q7 contains general guidance to industry on the extent and application of CGMP for manufacturing APIs under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the quality and purity characteristics that they purport or are represented to possess. ICH Q7 is to be used as a guideline for inspecting API manufacturers and related facilities. If an investigator believes that a particular practice conforming to this guidance is believed to be deficient, the investigator or district should consult with CDER DMPQ before making an observation that is in conflict with ICH Q7. A firm may also use alternate approaches to those described in ICH Q7.

API manufacturers must register and APIs in commercial distribution must be listed under section 510(g) of the Act unless exempted under 21 CFR 207.10. Foreign drug manufacturers are also required to register and list all drugs imported or offered for import into the United States. Refer to 21 CFR 207.40 for additional information on establishment registration and drug listing requirements for foreign drug facilities.

The inspection guidance in this program is structured for the efficient use of resources planned for routine surveillance coverage of API manufacturing facilities, recognizing that in-depth coverage of all systems and all processes is not feasible for all firms on a biennial basis. It also provides for follow-up compliance coverage as needed.

SCOPE OF APIs COVERED BY THIS PROGRAM

An API process is a related series of operations which result in the preparation of an active pharmaceutical ingredient. Major operations or steps in an API process may include multi-step chemical synthesis and fermentation, purification, crystallization, drying, milling, packing, labeling, and testing.

Some drugs processed similarly to an API may in fact be bulk finished product and subject to the requirements of 21 CFR Parts 210 and 211. If the drug material will not undergo further processing or compounding after its synthesis/fermentation/extraction, but is merely repackaged into market containers, it is a bulk finished product. However, investigators should use this program as guidance when covering the synthesis/fermentation processes that result in such APIs rather than the program for dosage forms (CP 7356.002).

This program does not cover all vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), and gene therapy APIs as these drugs are regulated under the jurisdiction of the Center for Biologics Evaluation and Research.

The following APIs are to be inspected using CP7256.002M, Inspections of Licensed Biological Therapeutic Drug Products:

- biotechnology-derived APIs, including those expressed from mammalian or bacterial cell cultures
- polypeptides

Neither this compliance program nor ICH Q7 will provide guidance on the sterilization and aseptic processing of sterile APIs (see Q7 Section 1.3). Investigators are to use the finished product regulations (21 CFR 210 and 211) as guidance and follow CP 7356.002A, *Sterile Drug Process Inspections*, when inspecting the sterile processing of APIs labeled as sterile. Investigators are also to use FDA guidance on aseptic processing, *Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice*, 2004, in evaluating aseptic processing conditions for sterile APIs.

[end Part I]

PART II - IMPLEMENTATION

OBJECTIVE

The primary objective of this compliance program is to provide comprehensive CGMP inspectional coverage of the domestic and foreign API industry in all profile classes (i.e., types of API manufacturing processes) to determine whether a manufacturer is operating in a state of control. An API manufacturer is considered to be operating in a state of control when it employs conditions and practices that assure compliance with the intent of Section 501(a)(2)(B) of the Act. A firm in a state of control produces APIs for which there is an adequate level of assurance of quality, identity and purity.

A firm is not in a sufficient state of control if any one system, as defined in this program, is found to be significantly non-compliant with CGMPs, such that the quality, identity and purity of the API resulting from that system cannot be adequately assured. Documented CGMP deficiencies provide the evidence for concluding that a system is not operating in a state of control. See Part V, *Regulatory/Administrative Strategy*, for a discussion of compliance actions based on inspection findings demonstrating that a system(s) is not in a state of control.

Profile classes generalize inspection coverage from a small number of specific APIs to all APIs in that class. This program establishes a systems approach to further generalize inspection coverage from a small number of profile classes to an overall evaluation of the firm. This allows for pre-approval program inspections to focus on the specific issues related to a given application and improves the review process by providing timely and efficient support for application decisions.

Inspection of API manufacturers should be conducted and reported using the system definitions and organization in this compliance program. Focusing on systems, rather than just profile classes, will increase efficiency in conducting inspections because the systems are often applicable to multiple profile classes. An inspection under this program is profileable and will result in a determination of acceptability/non-acceptability for all API profile classes. Inspection coverage should be representative of all API profile classes manufactured by the firm. All other profile classes should be covered under the main program CP 7356.002, or related program circular, as appropriate. Other objectives include:

- Obtain information on operations impacting on sterility, to identify areas for improvement and correction.
- Evaluate current good manufacturing practices in the sterile drug industry.
- Initiate appropriate action against manufacturers observed to be out of compliance.

PROGRAM MANAGEMENT INSTRUCTIONS

The Field will conduct API manufacturing inspections and maintain profiles or other monitoring systems with the goal that each API firm will receive biennial inspectional coverage. CDER will also identify firms for inspection coverage under this program to fulfill CDER and agency annual performance goals and as part of an initiative to ensure risk-based prioritization of inspection coverage.

Unless specifically directed by CDER, the District Office is responsible for determining the frequency and depth of coverage given to each API firm consistent with this compliance program's instructions. CGMP inspectional coverage under this program shall be sufficient to assess the state of compliance for each firm.

An inspection under this program is defined as audit coverage of 2 or more systems (the "systems" are defined below in this section and are consistent with the main program, 7356.002), with mandatory coverage of the Quality System. Inspecting at least two systems (i.e., the Quality System and one other system) will provide the basis for an overall CGMP decision.

Coverage of a system should be sufficiently detailed, with specific examples selected, so that the system inspection outcome reflects the state of control in that system for every profile class. If a particular representative system is adequate, it should be adequate for all profile classes manufactured by the firm.

If an API selected for inspection coverage is associated with a unique processing or control function in a system not chosen for coverage you may cover the unique function for that API. In doing so, you need not give full coverage to that system. For example, if an API chosen for coverage uses high purity water alone in its manufacture, you may inspect the water purification system without having to give full inspection coverage of the Materials System.

In some circumstances, it may not be possible to generalize certain deficiencies in a system to all API profile classes. If so, the unaffected profile classes may be considered acceptable if found otherwise acceptable.

Selecting unique functions within a system will be at the discretion of the investigator. Any given inspection need not cover every system.

Complete inspection of one system may necessitate further follow up of some aspects of another system to fully document the findings. However, this coverage does not constitute nor require complete coverage of the other system.

A general scheme of systems for auditing the manufacture of API consists of the following:

1. **Quality System** assures overall compliance with CGMPs and internal procedures and specifications.
2. **Facilities and Equipment System** includes activities which provide an appropriate physical environment and resources used in the production of APIs.
3. **Materials System** includes measures and activities to control starting materials, intermediates, and containers. It includes validation of computerized and inventory control processes, storage, and distribution controls.
4. **Production System** includes measures and activities to control the manufacture of APIs, including in-process sampling and testing, and process validation.
5. **Packaging and Labeling System** includes measures and activities that control the packaging and labeling of intermediates and APIs.

6. **Laboratory Control System** includes measures and activities related to laboratory procedures, testing, analytical methods development and methods validation or verification, and the stability program.

Detailed inspection coverage guidance under these systems is given in Appendix A of this program.

INSPECTION PLANNING

This program is intended to provide for a risk-based inspection strategy. Inspection depth should therefore reflect appropriate risks associated with a particular firm's operations, such as the firm's compliance history, the technology employed, the labeled and purported characteristics, and the intended use in the finished product, if known, of the APIs.

When a system is inspected, the inspection of that system may be considered applicable to all API products which use it. Investigators should select an adequate number and type of APIs to accomplish coverage of the system. APIs selected for coverage should be representative of the firm's overall abilities in manufacturing within CGMPs. (A profile classification scheme is used to categorize APIs by the nature of their processing, as described below.)

Profile class codes or APIs selected for coverage are to be representative of all APIs processed at the firm being inspected. Profile class codes may also be grouped by similarity, such that coverage of one profile class is sufficient to demonstrate CGMP conditions for another profile class. For example, inspecting a CSS API could amount to surrogate coverage of CSN. Similarly, inspecting a CBI could amount to surrogate coverage of other profile classes, such as CFN, CFS, and perhaps CEX.

The public health significance of certain CGMP deviations may be lower when the API is intended for a dosage form that has no dosage limitation, such as in products like calamine lotion or some OTC medicated shampoos. Such APIs should be given inspection coverage of reduced depth and intensity.

Profile Classes

The inspection findings will be used as the basis for updating all profile classes in the profile screen of the FACTS EIR coversheet that is used to record profile/class determinations. **Normally, an inspection under this system approach will result in all profile classes being updated**. Effective with this program circular are a list of profile class codes that are used to report the processes covered during API inspections. These are:

PROFILE CLASS	FULL DESCRIPTION
CBI	Biotechnology derived API (sterile and non-sterile)
CEX	Plant/Animal Extraction API
CFN	Non Sterile API by Fermentation
CFS	Sterile API by Fermentation
CRU	Non-sterile/intermediate/NEC inorganic/mineral (not plant/animal)
	(table continued on next page)

PROFILE CLASS	FULL DESCRIPTION
CRX	Sterile starting/intermediate/NEC (not plant/animal)
CSN	Non Sterile API by Chemical Synthesis
CSS	Sterile API by Chemical Synthesis
CTL	Control Testing Laboratory
CTX	Testing Laboratory plus Manufacturer
CXA	Purified API derived from plant/animal extraction

TYPES OF INSPECTIONS

There are two basic types of inspections: surveillance and compliance. Surveillance inspections are conducted on a routine basis to satisfy FDA's responsibilities to inspect drug manufacturing facilities. Compliance inspections are conducted in response to violative surveillance inspections and when a need arises to inspect a facility for-cause.

This program follows the approach in the main compliance program, 7356.002. There are two alternate approaches to inspecting a facility to satisfy FDA inspection obligations; these are termed "Full Inspection" and "Abbreviated Inspection." These are described in Part III, *Inspectional*, of this program.

[end Part II]

PART III - INSPECTIONAL

Inspections of API manufacturers, whether foreign or domestic, should be conducted by experienced investigators with education and/or training particularly in fermentation (see also 7356.002M for additional inspection guidance) and chemical synthesis manufacturing methods. Use of chemists and/or microbiologists during API inspections is recommended, particularly for evaluating laboratory operations (e.g., analytical methods evaluation, analytical data, lab procedures and instrumentation), analytical review of methods used to establish impurity profiles, fermentation manufacturing processes, and complex multi-step chemical synthesis processes.

Investigators conducting API inspections must understand the basic differences between the processes used for the production of APIs and those used for finished dosage forms. APIs are usually produced by chemical synthesis or by cell culture and extraction. Thus, the production of APIs typically involves significant changes of starting materials or intermediates by various chemical, physical, and biological processing steps. The ultimate objective in API processing generally is to achieve a pure compound of certain identity, whereas the ultimate objective of finished dosage form manufacturing generally is to achieve the uniform distribution of an API among many dosing units designed to deliver a precise amount of API to a specific area of the body.

Since manufacturers of APIs are often referenced in many drug applications, each inspection should cover representative APIs when covering the systems selected (e.g., if inspecting the Production System for a site making an API by fermentation and another by synthesis, the inspection should include physical inspection and audit a sampling of records for both types of processing). This strategy, together with the classification of all profile classes upon completion of the inspection, will maximize the use of agency resources and avoid repeated visits to the same manufacturing site to cover different API profile classes referenced in subsequent applications. Any inspection of an API manufacturer should be recorded as a CGMP qualifying inspection.

Inspections should cover any specific APIs referenced in the assignment and any other representative APIs not inspected in the last two years. For foreign API firms, investigators should cover only APIs intended to be marketed or already marketed in the United States.

APIs selected for coverage should include those that are referenced in drug applications, are therapeutically significant, are intended for use in parenteral drug products, are difficult to manufacture, or are documented as having past compliance problems. However, this does not preclude the selection of less therapeutically significant APIs to evaluate specific APIs (or profile classes) not previously given in-depth coverage at the facility.

Investigators conducting API inspections should understand the general inspection strategy set forth in this program. Recognizing that API firms vary greatly in size, diversity of operations, and quality assurance systems, investigators should carefully plan their inspectional strategy at each firm. Further guidance on preparing an inspection strategy appears later.

Investigators should also review the firm's rationale for the point at which CGMPs begin, which is expected to vary by type of process (e.g., synthetic, fermentation, extraction, purification).

For an API inspection that is initiated by a pre-approval assignment, CP 7346.832, *Pre-Approval Inspections/Investigations*, inspection time should be reported under the appropriate program assignment codes referenced in both compliance programs based on the actual time spent in each program.

INSPECTION APPROACHES

This program provides two surveillance inspectional options: Full Inspection Option and Abbreviated Inspection Option. Either option may satisfy the biennial inspection requirement.

Full Inspection Option

The Full Inspection Option is a surveillance or compliance inspection which is meant to provide a broad and in-depth evaluation of the firm's conformity to CGMPs. The Full Inspection Option is an inspection of at least four of the six systems as listed in Part II and Appendix A of this program, one of which must be the Quality System.

A Full Inspection is appropriate:

a. For an initial FDA inspection of a facility, or after a significant change in management or organizational procedures, such as might occur after a change in ownership.

b. For a firm with a history of non-compliance or a recidivist firm whose ability to comply is short-lived. To determine if the firm meets this criterion, the District should utilize all information at its disposal, such as current and past inspection findings, results of sample analyses, complaints, recalls, and compliance actions.

c. To evaluate if important changes have occurred in the firm's state of control by comparing current operations against the EIR for the previous Full Inspection (e.g., by conducting a Full Inspection at every fourth inspection cycle.) In addition to changes in management or ownership, the following types of changes are typical of those that warrant the Full Inspection Option:

   i. New potential for cross-contamination arising through changes in processing or type of PIs using that equipment.

   ii. Use of new technology requiring new expertise, significant equipment changes and/or additions, or new facilities.

d. When District management or CDER specifically requests this option.

e. To follow up on a Warning Letter or other regulatory action.

Abbreviated Inspection Option

The Abbreviated Inspection Option is a surveillance or compliance inspection which is meant to provide an efficient update evaluation of the firm's conformity to CGMPs. A satisfactory Abbreviated Inspection will provide documentation for continuing a firm in an acceptable CGMP compliance status. The Abbreviated Inspection Option is an inspection audit of at least two systems but not more than three systems, one of which must be the Quality System. During the course of an Abbreviated Inspection, verification of Quality System activities may require limited coverage in other systems.

An Abbreviated Inspection is appropriate when the Full Inspection Option is not warranted, including:

a. To maintain surveillance over a historically compliant firm's activities and to provide input to the firm on maintaining and improving the CGMP level of assurance of quality of its APIs.

b. When an intended Full Inspection finds objectionable conditions as listed in Part V of this program in one or more systems (a minimum of two systems must be completed) and District management and, as necessary, CDER Office of Compliance, concurs with reducing inspection coverage in order to expedite the issuance of a Warning Letter to correct violations.

Compliance Inspections

Compliance Inspections are inspections done "for-cause" and to evaluate or verify corrective actions after a regulatory action has been taken. The coverage given in compliance inspections must be related to the areas found deficient and subjected to corrective actions.

In addition, coverage must be given to other systems because a determination must be made on the overall compliance status of the firm after the corrective actions are taken. The firm is expected to address all of its operations in its corrective action plan after a previously violative inspection, not just the deficiencies noted in the FDA-483. The Full Inspection Option should be used for a compliance inspection, especially if the Abbreviated Inspection Option was used during the violative inspection.

Compliance Inspections include "For-Cause Inspections." For-Cause Inspections are for the purpose of investigating a specific problem that has come to the attention of the agency and may not result in the coverage of systems as described in this program. The problem may be identified by a complaint, recall, or other indicator of defective API or poorly controlled process. Coverage of these problems may be assigned under other compliance programs or PACs; however, expansion of the coverage to a CGMP inspection is to be reported under this program. For-Cause Inspections may be assigned under this program as the need arises.

SELECTING SYSTEMS FOR COVERAGE

A complete description of each system and the areas for coverage are in Appendix A of this program. The selection of the system(s) for coverage and the relative depth or intensity of audit

coverage should take into consideration the relative significance of a particular system for the firm's specific operating conditions, history of previous coverage, and history of CGMP compliance. It is expected that a Full Inspection will not be conducted every two years at most firms. Districts should select different systems for inspection coverage as a cycle of Abbreviated Inspections is carried out to build comprehensive information on the firm's total manufacturing activities over time.

PREPARING THE INSPECTION STRATEGY

This guidance is in addition to that given in the *Investigations Operations Manual* (IOM).

1. Select two or more, as appropriate, systems for inspection coverage as guided by this program (see *Inspection Approaches*, above). *Appendix A* contains a detailed description of the inspection coverage to be given each system when selected for inspection.

2. Select significant APIs for inspection coverage, if not specified in the assignment. Significant APIs are those which utilize all the systems in the firm very broadly and/or use special manufacturing features, e.g., complex chemical synthesis, highly sensitizing material, material of an infectious nature, or a new chemical entity made under an approved drug application. Review the firm's FACTS listing, Drug Master Files (DMF) or A/NDA files.

3. If a CDER product or CGMP/regulatory reviewer (compliance officer) is assigned to participate as a member of the inspection team, the lead investigator is to brief them on the intended inspection strategy and explain their supporting role and responsibilities for the inspection. The lead investigator should consult the reviewer on any specific A/NDA chemistry, manufacturing and controls issues (whether pre-market or post-market) to be covered during the inspection.

4. Review the impurity profile for each API process to be covered during the inspection and compare these to the impurity profiles submitted in the application or DMF, if filed. (Investigators and Chemists should be particularly familiar with USP <1086> *Impurities in Official Articles*.) If the impurity profile has not been filed to CDER, review the guidance on establishing impurity profiles in ICH Q3A and Q3C.

5. Review any compendia monographs for the APIs to be inspected to verify conformity, as appropriate.

6. Before or during the inspection, determine if the firm has made process changes by comparing current operations against the EIR for the previous inspection. Also compare the current operations with those filed in the DMF or the drug application to determine whether the firm is complying with commitments made to the agency. (See also CP 7346.832 for conducting a pre-approval inspection of an API.) The following changes are typical of those that would warrant extensive coverage during the inspection:

a. New potential for cross-contamination arising through changes in API processes or product-type lines, to include processing numerous APIs of varying toxicity in common equipment and/or facilities.

b. Use of new technology requiring new expertise, significantly new equipment or new facilities.

c. Changes in starting materials, intermediates, equipment, facilities, support systems, processing steps, packaging materials, or computer software, particularly those that are not referenced in the DMF or application.

7. For foreign firms, Division of Medical Products and Tobacco Inspections (DMPTI) will assist investigators in obtaining file information from the appropriate CDER reviewing division or compliance unit. Investigators may also request background information about the site assigned for inspection directly from the US Agent before the initiation of the inspection.

SPECIAL INSPECTION REPORTING INSTRUCTIONS:

Investigators should describe in the EIR their inspection coverage and findings in sufficient detail for further agency evaluation of the firm's state of control and conformance to CGMPs. ICH Q7 may be used as a guideline in describing coverage and any findings and deficiencies observed. However, do not reference specific ICH Q7 sections in the FDA 483 observations or in the EIR. The FDA 483, if issued, is to be organized into sections for each of the systems covered. In addition to the IOM format and information reporting requirements, all EIRs of API manufacturers must include:

1. A list of APIs manufactured (or categories of drugs, if many) along with the general manufacturing process for each (e.g., chemical synthesis, fermentation, extraction of botanical material).

2. For foreign API manufacturers, the names, titles, complete mailing address, telephone and fax number of the firm's U.S. Agent.

3. For foreign API manufacturers, a report of all APIs imported into the United States in the last two years, their consignees, and an estimate of the frequency and quantity of shipments to these consignees.

4. A description of each of the systems selected for coverage, (i.e., areas, processes, and operations), what was covered, who was interviewed, and what manufacturing activities were taking place during the inspection.

5. An explanation of the choice of APIs selected for coverage.

6. Any significant changes to a firm's packaging, labeling, product line, or processes, particularly those changes not properly filed, submitted, or reported in a DMF or A/NDA.

SPECIAL INSTRUCTIONS FOR FOREIGN DRUG INSPECTIONS

The Office of Medical Products and Tobacco Operations (OPMTO) schedules foreign inspections, makes travel arrangements for inspection teams, and resolves logistical problems. CDER's Office of Pharmaceutical Quality/ Office of Quality Surveillance OPQ/OQS receives and reviews all foreign establishment inspection reports, receives and reviews all foreign firms' responses to an FDA 483, and handles all correspondence regarding inspection outcomes with foreign firms. CDER/OPQ/OQS maintains the complete file for each foreign drug facility.

Investigators should instruct management at foreign firms to submit their original written response to an FDA 483 directly to CDER OPQ/OQS, with a copy to the investigator. The original response with appropriate documentation should be submitted via email to CDEROSIAB@FDA.HHS.GOV

or to the following address:

Food and Drug Administration
Office of Quality Surveillance
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Building 51, Room 4316
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002
USA

Investigators and analysts are to submit their written comments to a foreign firm's response to their issued FDA 483 directly to OPQ/OQS as soon as possible. After appropriate district office review and endorsement, all foreign establishment inspection reports will be promptly forwarded to OPQ/OQS for review and final classification.

CDER Office of Compliance (OC), Office of Manufacturing Quality (OMQ) will draft and coordinate the issuance of Warning Letters, Untitled Letters, and other correspondence to foreign firms. OC/OMQ will also recommend automatic detention of foreign firms/APIs, make recommendations to review units, and request follow-up inspections, as appropriate.

[end Part III]

PART IV - ANALYTICAL

API samples collected by the investigator for the purpose of evaluating quality are to be submitted to the appropriate servicing laboratory. A list of each analyzing laboratory for API testing is maintained in Compliance Programs 7356.002 and 7346.832. However, it should be noted that physical API samples are not required to support regulatory or administrative action against a violative firm or drug.

Forensic Chemistry Center (FCC) will request profile (also called "forensic" and "fingerprint") samples of both foreign and domestic source APIs directly from the manufacturer. Investigators are to collect API samples for profile analysis only upon specific request for collection from FCC. Such requests will be made through DMPTPO. If an investigator is instructed to collect a profile sample, FCC will provide specific instructions as to method and amount of collection and shipping. FCC contact information is in Part VI, *Program Contacts*.

Prior to each foreign API site inspection, DMPTPO will provide FCC with the inspection dates, the investigator's name, firm's name, address, telephone number, fax number, FEI number, any related product and application numbers, and the name of the contact person. FCC will then directly request a sample from the firm as needed. FCC may contact the investigator to request their collection of any specific information. The inspection dates will provide FCC information, so they can access FACTS to obtain the EIR coversheet.

FCC is responsible for API profile sample collection and analysis and will provide periodic reports of such analysis and assist CDER in evaluating this program's effectiveness.

[end Part IV]

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

An inspection report that documents that one or more systems is out of control should be classified OAI. Districts may recommend the issuance of a warning letter in accordance with the RPM. Normally, the issuance of a warning letter or the taking of other regulatory or administrative action should result in a classification of all profile classes as unacceptable. A CDER disapproval of a recommendation for warning letter or other regulatory action should result in a classification of all profile classes as acceptable.

A warning letter with a CGMP charge (i.e., 501(a)(2)(B) adulteration) involving a domestic API manufacturer requires CDER review and concurrence before issuance. See and follow *FDA Regulatory Procedures Manual* procedures for clearing warning letters and untitled letters.

A recommendation for regulatory action for API CGMP deficiencies is to cite the statute (501(a)(2)(B) or United States Code, 21 USC 351(a)(2)(B)) and not the finished pharmaceutical regulations at 21 CFR 210 and 211. A recommendation should also not cite to ICH Q7, but may use ICH Q7 as a guideline in describing the deficiencies observed. Any regulatory action based upon CGMP noncompliance for APIs should demonstrate how the observed deviations could or did result in actual or potential defects or risk to contamination. In evaluating whether to recommend regulatory or administrative action, consider the critical attributes of the API, its therapeutic significance, and its intended use in finished drug product manufacturing.

Evidence that supports a significant deficiency or pattern of deficiencies within a system may demonstrate the failure of a system. A failure of a system puts all drugs at risk and is to be promptly corrected. The following lists the deficiencies that should result in a recommendation for regulatory action to CDER; other deficiencies may also warrant regulatory action:

1. Contamination of APIs with filth, objectionable microorganisms, toxic chemicals, or significant amounts of other types of chemicals, or a reasonable potential for such contamination because of a finding of a demonstrated route of contamination. (Facilities and Equipment System; Production System)

2. Failure to show that API batches conform to established specifications, such as NDA, USP, customer specifications, and label claims. See also Compliance Policy Guide (CPG) 7132.05. (Quality System)

3. Failure to comply with commitments in drug applications, including DMFs, which should be accurate and current with respect to all required information, such as manufacturing process, impurity profiles (if filed), and other specifications or procedures associated with the manufacture of the API. (Quality System)

4. Distribution of an API that does not conform to established specifications. (Quality System)

5. Deliberate blending of API batches to dilute or hide filth or other noxious contaminants, or blending to disguise a critical quality defect in an attempt to obtain a batch that meets its specifications. (Production System)

6. Failure to demonstrate that water, including validation of the process water purification system, and any other solvents used in the final step of the API process are chemically and microbiologically suitable for their intended use and does not adversely alter the quality of the API. (Materials System)

7. Lack of adequate validation of critical steps in the API process, particularly concerning final separation and purification of the API, or when there is evidence that an API process is not adequately controlled. Lack of adequate control may be indicated by repeated batch failures or wide variation in final yields as compared to process average over time. See also the revised CPG 7132c.08, *Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval*. (Quality System; Production System)

8. Implementation of retrospective process validation for an existing API process when the process has changed significantly, when the firm lacks impurity profile data, or when there is evidence of repeated batch failures due to process variability. (Quality System; Production System)

9. Failure to establish an impurity profile for each API process. FDA expects manufactures to establish complete impurity profiles for each API as part of the process validation effort. This includes collecting data on (1) actual and potential organic impurities that may arise during synthesis, purification, and storage of the API; (2) inorganic impurities that may derive from the API process; and (3) organic and inorganic solvents used during the manufacturing process that are known to carry over to the API. Impurity profile testing of each batch or after a specified number of batches may detect new impurities that may appear because of a deliberate or non-deliberate change in the API manufacturing process. (Laboratory Control System)

10. Failure to show that a reprocessed batch complies with all established standards, specifications, and characteristics. (Quality System; Laboratory Control System)

11. Failure to test for residues of organic/inorganic solvents used during manufacturing that may carry over to the API using analytical procedures with appropriate levels of sensitivity. (Laboratory Control System)

12. Failure to have a formal process change control system in place to evaluate changes in starting materials, facilities, support systems, equipment, processing steps, and packaging materials that may affect the quality of APIs. (All systems)

13. Failure to maintain batch and quality control records. (Quality System)

14. Incomplete stability studies to establish API stability for the intended period of use, and/or failure to conduct forced degradation studies on APIs to isolate, identify and

quantify potential degradants that may arise during storage. (Laboratory Control System)

15. Use of laboratory test methods that are inadequate or have not been validated; or, the use of an inadequately qualified or untraceable reference standard. (Laboratory Control System)

16. Packaging and labeling in such a way that introduces a significant risk of mislabeling. (Packaging and Labeling System)

[end Part V]

PART VI - REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

REFERENCES

Note regarding Guidance for Industry: Please review the guidance document posted at FDA's website to ensure you use the current version. FDA guidance documents, including ICH guidance, are here:
[http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm]

1. ICH Guidance for Industry: Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, August 2001
2. ICH Guidance for Industry: Q11 *Development and Manufacture of Drug Substances*
3. ICH Q3A *Impurities in New Drug Substances*
4. ICH Q3C *Impurities: Residual Solvents*, and appendices
5. Compliance Program 7356.002, Drug Manufacturing Inspections, and related programs
https://www.fda.gov/media/75167/download
6. Compliance Policy Guide 490.100 (7132c.08), Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval
[http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/default.htm]
7. Compliance Policy Guide 420.400 (7132.05), Performance of Tests for Compendial Requirements on Compendial Products
[http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/default.htm]
8. The United States Pharmacopoeia / National Formulary (USP/NF) - available on-line through WebLERN
9. FDA Regulatory Procedures Manual
[http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/default.htm]

ATTACHMENTS – none.

PROGRAM CONTACTS

Center for Drug Evaluation and Research (CDER)

CGMP or any Quality-Related Policy Questions
For CGMP or any quality-related policy question, technical or scientific questions or information needs, including questions about this program, please send an email to the following address and it will be handled as a top priority:

CDER-OPQ-Inquiries@fda.hhs.gov

Enforcement-Related Guidance or Policy
For enforcement-related guidance or policy, including evidence need and sufficiency, citations, and case evaluation/recommendation advice, please send an email to the following address and it will be handled as a top priority:

CDER OMQ Compliance Policy: CDEROMQCompliance@fda.hhs.gov

Labeling Requirements and Policies

Office of Unapproved Drugs and Labeling Compliance, see intranet home page for contacts
[CDER | Office of Compliance | Office of Unapproved Drugs and Labeling Compliance]

Registration and Drug Listing Requirements
CDER Office of Compliance, see "CDER: Who's the Lead" intranet page for contacts
[CDER | Office of Communications | CDER: Who's the Lead]

Office of Regulatory Affairs (ORA)

For questions on profile sampling of APIs: Food and Drug Administration

Forensic Chemistry Center (HFR-MA500)
Bulk Drug Group
6751 Steger Dr.
Cincinnati, Ohio 45237-3097
Telephone: (513) 679-2700, extension 185 or 181
Fax: (513) 679-2761

Office of Medical Products and Tobacco Operations (OMPTO)

Division of Medical Products and Tobacco Program Operations
(OMPTO/DMPTPO)
Telephone: (301) 796-0358
Email: ORAHQDrugInspectionPOC@fda.hhs.gov

Office of Regulatory Science
(ORS)
Telephone: (301) 796-7057
Fax: (301) 827-9806

Office of Enforcement and Import Operations (OEIO)

Telephone: (301) 796-5270
Fax: (301) 827-3631

[end Part VI]

PART VII - CENTER RESPONSIBILITIES

Center responsibilities are as described in *Drug Manufacturing Inspections* Compliance Program 7356.002 and *Pre-Approval Inspection/Investigations* Compliance Program 7346.832

[end Part VII]

APPENDIX A: Description of Each System and Areas of Coverage

QUALITY SYSTEM

Assessment of the Quality System has two phases. The first phase is to evaluate whether the Quality Unit has fulfilled the responsibility to review and approve all procedures related to production, quality control, and quality assurance and assure the procedures are adequate for their intended use. This also includes the associated recordkeeping systems. The second phase is to assess the data collected to identify quality problems and may link to other major systems for inspectional coverage.

For each of the following bulleted items, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to the final API's, but may also include starting materials and intermediates. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. All areas under this system should be covered; however the actual depth of coverage may vary from the planned inspection strategy depending upon inspectional findings.

- Adequacy of staffing to ensure fulfillment of quality unit duties
- Periodic quality reviews as described in ICH Q7 Section 2.5, *Product Quality Review*; inspection audit coverage should include API types that are representative of manufacturing at this site; inspection audit should also examine some batch and data records associated with each API quality review to verify that firm's review was sufficiently complete; and, audit should confirm that firm has identified any trends and has corrected or mitigated sources of unacceptable variation.
- Complaint reviews (quality and medical): documented; evaluated; investigated in a timely manner; includes corrective action where appropriate. Determine whether pattern of complaints and records of internal rejection or reprocessing/reworking of API batches warrant expanding the inspection.
- Discrepancy and failure investigations related to manufacturing and testing: documented; evaluated; critical deviations investigated in a timely manner and expanded to include any related APIs and material; includes corrective action where appropriate.
- Change Control (including "process improvements"): documented; evaluated; approved; need for revalidation assessed.
- Returns/Salvages: assessment; investigation expanded where warranted; final disposition.
- Rejects: investigation expanded where warranted; corrective action where appropriate.
- System to release raw materials.
- Batches manufactured since last inspection to evaluate any rejections or conversions (i.e., from drug to non-drug use) due to processing problems.
- Reprocessing and/or reworking events are properly approved and evaluated for impact on material quality.
- Recalls (including any attempt to recover distributed API not meeting its specifications or purported quality), determine cause and corrective actions taken.
- Stability Failures: investigation expanded where warranted; disposition. Determine if stability data supports API retest or expiry dates and storage conditions.

- Validation: Status of validation/revalidation activities (e.g., computer, manufacturing process, laboratory methods), such as reviews and approvals of validation protocols and reports.
- Training/qualification of employees in quality control unit functions.

ICH Q7 references for **Quality System**:

- Section 2, *Quality Management*
- Section 13, *Change Control*
- Section 14, *Rejection and Reuse of Materials*
- Section 15, *Complaints and Recalls*
- Section 16, Contract Manufacturers (including laboratories).

FACILITIES AND EQUIPMENT SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed below should be covered; however, the actual depth of coverage may vary from the planned inspection strategy depending upon inspectional findings.

1. Facilities

- Cleaning and maintenance.
- Facility layout, flow of materials and personnel for prevention of cross-contamination, including from processing of non-drug materials.
- Dedicated areas or containment controls for highly sensitizing materials (e.g., penicillin, beta- lactams, steroids, hormones, and cytotoxics).
- Utilities such as steam, gas, compressed air, heating, ventilation, and air conditioning should be qualified and appropriately monitored (note: this system includes only those utilities whose output is not intended to be incorporated into the API, such as water used in cooling/heating jacketed vessels).
- Lighting, sewage and refuse disposal, washing and toilet facilities.
- Control system for implementing changes in the building.
- Sanitation of the building including use of rodenticides, fungicides, insecticides, cleaning and sanitizing agents.
- Training and qualification of personnel.

2. Process Equipment

- Equipment installation, operational, performance qualification where appropriate.
- Appropriate design, adequate size and suitably located for its intended use.
- Equipment surfaces should not be reactive, additive, or absorptive of materials under process so as to alter their quality.
- Equipment (e.g., reactors, storage containers) and permanently installed processing lines should be appropriately identified.

- Substances associated with the operation of equipment (e.g., lubricants, heating fluids or coolants) should not come into contact with starting materials, intermediates, final APIs, and containers.
- Cleaning procedures and cleaning validation and sanitization studies should be reviewed to verify that residues, microbial, and, when appropriate, endotoxin contamination are removed to below scientifically appropriate levels.
- Calibrations using standards traceable to certified standards, preferably NIST, USP, or counterpart recognized national government standard-setting authority.
- Equipment qualification, calibration and maintenance, including computer qualification/validation and security.
- Control system for implementing changes in the equipment.
- Documentation of any discrepancy (a critical discrepancy investigation is covered under the Quality System).
- Training and qualification of personnel.

ICH Q7 references for **Facilities and Equipment System**:

- Section 4, *Buildings and Facilities*
- Section 5, *Process Equipment*
- Section 6, *Documentation and Records*

MATERIALS SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to the final API, but may also incorporate starting materials and intermediates. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed below should be covered; however, the actual depth of coverage may vary from the planned inspection strategy depending upon inspectional findings.

- Training/qualification of personnel.
- Identification of starting materials, containers.
- Storage conditions.
- Holding of all material and APIs, including reprocessed material, under quarantine until tested or examined and released.
- Representative samples are collected, tested or examined using appropriate means and against appropriate specifications.
- A system for evaluating the suppliers of critical materials.
- Rejection of any starting material, intermediate, or container not meeting acceptance requirement.
- Appropriate retesting/reexamination of starting materials, intermediates, or containers.
- First-in / first-out use of materials and containers.
- Quarantine and timely disposition of rejected materials.
- Suitability of process water used in the manufacture of API, including as appropriate the water system design, maintenance, validation and operation.

- Suitability of process gas used in the manufacture of API (e.g., gas use to sparge a reactor), including as appropriate the gas system design, maintenance, validation and operation.
- Containers and closures should not be additive, reactive, or absorptive.
- Control system for implementing changes.
- Qualification/validation and security of computerized or automated process.
- Finished API distribution records by batch.
- Documentation of any discrepancy (a critical discrepancy investigation is covered under the Quality System).

ICH Q7 references for **Materials System**:

- Section 7, *Materials Management*
- Section 10, *Storage and Distribution*
- Section 4.3, *Water*
- Section 6, *Documentation and Records*

PRODUCTION SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to the final API, but may also incorporate starting materials and intermediates. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed below should be covered; however, the actual depth of coverage may vary from the planned inspection strategy depending upon inspectional findings.

- Training/qualification of personnel.
- Establishment, adherence, and documented performance of approved manufacturing procedures.
- Control system for implementing changes to process.
- Controls over critical activities and operations.
- Documentation and investigation of critical deviations.
- Actual yields compared with expected yields at designated steps.
- Where appropriate established time limits for completion of phases of production.
- Appropriate identification of major equipment used in production of intermediates and API.
- Justification and consistency of intermediate specifications and API specification.
- Implementation and documentation of process controls, testing, and examinations (e.g., pH, temperature, purity, actual yields, clarity).
- In-process sampling should be conducted using procedures designed to prevent contamination of the sampled material.
- Recovery (e.g., from mother liquor or filtrates) of reactants; approved procedures and recovered materials meet specifications suitable for their intended use.
- Solvents can be recovered and reused in the same processes or in different processes provided that solvents meet appropriate standards before reuse or commingling.

- API micronization on multi-use equipment and the precautions taken by the firm to prevent or minimize the potential for cross-contamination.
- Process validation, including validation and security of computerized or automated process
- Master batch production and control records.
- Batch production and control records.
- Documentation of any discrepancy (a critical discrepancy investigation is covered under the Quality System).

ICH Q7 references for **Production System**:

- Section 6, *Documentation and Records*
- Section 8, *Production and In-Process Controls*
- Section 12, *Validation*
- Section 18, *Specific Guidance for APIs Manufactured by Cell Culture / Fermentation*

See also Compliance Program 7356.0002M for additional inspection guidance on fermentation, extraction, and purification processes.

PACKAGING AND LABELING SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to the final API, but may also incorporate starting materials and intermediates. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed below should be covered; however, the actual depth of coverage may vary from the planned inspection strategy depending upon inspectional findings.

- Training/qualification of personnel.
- Acceptance operations for packaging and labeling materials.
- Control system for implementing changes in packaging and labeling operations
- Adequate storage for labels and labeling, both approved and returned after issued.
- Control of labels which are similar in size, shape, and color for different APIs.
- Adequate packaging records that will include specimens of all labels used.
- Control of issuance of labeling, examination of issued labels and reconciliation of used labels.
- Examination of the labeled finished APIs.
- Adequate inspection (proofing) of incoming labeling.
- Use of lot numbers, destruction of excess labeling bearing lot/control numbers.
- Adequate separation and controls when labeling more than one batch at a time.
- Adequate expiration or retest dates on the label.
- Validation of packaging and labeling operations including validation and security of computerized process.
- Documentation of any discrepancy (a critical discrepancy investigation is covered under the Quality System).

ICH Q7 references for **Packaging and Labeling System**

- Section 9, *Packaging and Identification Labeling of APIs and Intermediates*
- Section 17, *Agents, Brokers, Traders, Distributors, Repackers, and Relabellers* (applies to the handling of APIs after original site of manufacture and before receipt by the dosage manufacturer)

LABORATORY CONTROL SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to the final API, but may also incorporate starting materials and intermediates. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed below should be covered; however, the actual depth of coverage may vary from the planned inspection strategy depending upon inspectional findings.

- Training/qualification of personnel.
- Adequacy of staffing for laboratory operations.
- Adequacy of equipment and facility for intended use.
- Calibration and maintenance programs for analytical instruments and equipment.
- Validation and security of computerized or automated processes.
- Reference standards; source, purity and assay, and tests to establish equivalency to current official reference standards as appropriate.
- System suitability checks on chromatographic systems.
- Specifications, standards, and representative sampling plans.
- Validation/verification of analytical methods.
- Required testing is performed on the correct samples and by the approved or filed methods or equivalent methods.
- Documentation of any discrepancy (a critical discrepancy investigation is covered under the Quality System).
- Complete analytical records from all tests and summaries of results.
- Quality and retention of raw data (e.g., chromatograms and spectra).
- Correlation of result summaries to raw data; presence and disposition of unused data.
- Adherence to an adequate Out of Specification (OOS) procedure which includes timely completion of the investigation.
- Test methods for establishing a complete impurity profile for each API process (note: impurity profiles are often process-related).
- Adequate reserve samples; documentation of reserve samples examination.
- Stability testing program, including demonstration of stability indicating capability of the test methods.

ICH Q7 references for **Laboratory System**:

- Section 11, *Laboratory Controls*
- Section 6, *Documentation and Records*
- Section 12, *Validation*

ICH Q7 Sections 3, *Personnel,* and 6, *Documentation and Records,* apply to all systems. Section 19, *APIs for Use in Clinical Trials,* applies to APIs intended for the production of dosages solely for use in a clinical trial.

The organization and personnel, including appropriate qualifications and training, employed in any given system, will be evaluated as part of that system's operation. Production, control, or distribution records are required to maintain CGMPs and those selected for review should be included for inspection audit within the context of each of the above systems. Inspection of contract companies should be within the system for which the intermediate or API, or service is contracted and also include evaluation of their Quality System.

[end Appendix A]

Exhibit 24

FDA STATEMENT

FDA Statement on FDA's ongoing investigation into valsartan impurities and recalls and an update on FDA's current findings

For Immediate Release:

August 30, 2018

Statement From:

Scott Gottlieb, M.D.

Millions of Americans take medication daily to control their blood pressure. We recently found that some generic versions of one medication, valsartan, contain an impurity that doesn't meet FDA's safety standards. Valsartan is an angiotensin II receptor blocker (ARB) that treats high blood pressure and heart failure. The FDA currently has a major operation underway to investigate and address this troubling finding. This investigation is led by a dedicated task force of experts focused solely on this important work. Their mandate is to oversee the investigation and track new developments and information coming in from valsartan manufacturers. This multidisciplinary team of chemists, toxicologists, medical doctors, pharmacists, investigators, communication specialists, and analytical lab staff coordinates across the FDA, and acts on the newest available information.

As our investigation continues to identify the root cause of this impurity, we want to take the opportunity to describe to the public what we are doing to find the cause of the impurity, to prevent a recurrence of this episode and to protect patients who need this medication.

On June 19, a U.S. manufacturer of valsartan products, Prinston Pharmaceuticals Inc., contacted the FDA's Center for Drug Evaluation and Research (CDER) about its products containing valsartan active pharmaceutical ingredient (API) manufactured by Zhejiang Huahai Pharmaceutical Co. (ZHP). Prinston informed CDER that they had stopped making valsartan products because ZHP had detected an impurity in the API – a chemical known as N-nitrosodimethylamine (NDMA). NDMA is a probable cancer-causing chemical found in trace amounts in water and some foods. However, the levels of NDMA in ZHP's valsartan API – while still trace amounts – were unacceptable.

Although the risk to patients taking the affected products is extremely low, we take matters of pharmaceutical quality very seriously. We took immediate steps to address these findings.

Shortly after initiating our investigation, we learned that a foreign regulator was also reviewing medications containing valsartan API manufactured by ZHP and considering a recall. We have closely coordinated with the European Medicines Agency, European Directorate for the Quality of Medicines, Regulatory Operations and Regions Branch and Therapeutic Products Directorate of Health Canada, and the Pharmaceuticals and Medical Devices Agency in Japan since that time, sharing information about our investigation with them and other regulatory bodies and learning about their findings.

We recognized that we had to find answers to several important questions: How many U.S. valsartan products are affected? Where did the impurity come from? What are the potential health consequences of the impurity? How many patients are affected? How long have patients been exposed to NDMA? How do we ensure that patients and providers are informed so that health care is minimally disrupted? How do we prevent drug shortages? And could similar drugs also contain this impurity?

Our first priority was to inform patients and health care providers. To do this, we had to verify the information about ZHP's API to understand the risk to U.S. patients and the scope of APIs and products potentially affected by this impurity. We identified four manufacturers using valsartan API from ZHP for the U.S. market. We contacted them to ask if they knew about NDMA in their products and to recommend recalls of affected products. In addition to ZHP, we identified 13 other API manufacturers who supply more than 20 drug companies that make valsartan for the U.S. market. We made plans to determine if their products could also contain NDMA.

By July 13, we had the information we needed to issue a press release (/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity) stating that three companies had products containing NDMA and were voluntarily recalling them. One of the four manufacturers we initially identified required further investigation, but has since voluntarily recalled (/drugs/drug-safety-and-availability/fda-updates-valsartan-recalls) its products.

However, we did not want patients taking valsartan to hear this news and abruptly stop their medications, possibly suffering serious medical issues, such as stroke. We needed to let patients know the specific products impacted by the recalls, so they could talk to their health care providers and get prescriptions for products that had not been recalled. We began posting frequent updates to our website, listing first the valsartan products affected by the recall (/media/115390/download), followed by a list of the hundreds of products not affected (/media/115393/download) at that time. We shared this information broadly across other communication channels known to reach consumers and health care providers, such as social media, newswires and email listservs. Because this is a continuing investigation, more manufacturers may discover that their valsartan products contain NDMA and take steps to voluntarily recall them. We encourage patients and prescribers to check these lists frequently for potential changes in the recall status of their medicine. We are continuing to update this information on a regular basis and update consumers over our social media platforms to ensure broad reach.

CDER toxicologists and chemists evaluated the risk to the public. On July 27, we shared (/drugs/drug-safety-and-availability/fda-updates-valsartan-recalls) what our scientists were able to estimate was the theoretical risk that the impurity could pose to patients. We estimated that if 8,000 people took the highest valsartan dose (320 mg) from NDMA-affected medicines daily for four years (the amount of time we believed the affected products had been on the U.S. market), there may be one additional case of cancer over the lifetimes of these 8,000 people beyond the average cancer rate among Americans. This estimate represented the highest possible level of NDMA exposure. It was a measure of the risk under the most extreme circumstances. Most patients who were exposed to the impurity through the use of valsartan received less exposure than this worst-case scenario.

In St. Louis, the FDA maintains the most advanced pharmaceutical laboratory of any regulatory agency in the world. As soon as we were aware of the NDMA impurity in certain valsartan drugs, we began collecting samples of all valsartan API and products marketed in the U.S. At the same time, our scientists began developing a test to detect and quantify NDMA in valsartan API. NDMA's properties make it difficult to find. To determine if valsartan products do contain this impurity, CDER's scientists have now developed the gas chromatography-mass spectrometry (GC/MS) headspace testing method. We posted (/files/drugs/published/GC-MS-Headspace-Preliminary-Method-for-Detection-of-NDMA-in-Valsartan-Drug-Substance.pdf) this method to the web to help manufacturers and regulators detect NDMA in valsartan API and tablets.

Based on information provided regarding ZHP's manufacturing processes, we believed (but did not have proof) that the impurity resulted from changes that ZHP made to the manufacturing process for its API. We needed to identify the root cause of the problem and evaluate ZHP's explanation. After assessing information about ZHP's manufacturing processes and the changes ZHP made over time, we identified how its processes could have led to the presence of NDMA in their API.

Specifically, a combination of conditions, which include certain chemicals, processing conditions and production steps, could lead to formation of the NDMA impurity. We believe that these risks are introduced through a specific sequence of steps in the manufacturing process, where certain chemical reactions are needed to form the active ingredient. Before we undertook this analysis, neither regulators nor industry fully understood how NDMA could form during this process. We are still not 100 percent sure that this is the root cause of the problem. Full understanding will require correlation of multiple test results from valsartan APIs made by different processes with the various process steps used by different manufacturers or at different times. We need to determine how NDMA can be formed and why it is not separated from the API during purification.

Once we understand the way or ways that the NDMA impurity can occur as a by-product of the manufacturing process, we will make sure these conditions are evaluated in API synthetic processes so that, in the future, testing for this impurity would be required if there was a risk of NDMA formation.

NDMA is one chemical in a class called "genotoxic impurities". These chemicals are of special concern to global regulators because, unlike most impurities in drugs, they have the potential to cause harm at very low levels. The FDA has worked with international regulators to create standards for mitigating the risk of such impurities. We have robust policies and procedures in place to guard against these risks.

The FDA will continue to improve its procedures for guarding against these impurity risks. We will use the information that we learn from our investigation into valsartan to strengthen our oversight.

In March 2018, the FDA issued a guidance (/media/85885/download) for manufacturers that lays out risk assessements that manufacturers can use to evaluate the presence of genotoxic impurities. This is an internationally-harmonized guidance that both regulators and industry have agreed to. To implement the risk assessment for any genotoxic impurity, there has to be recognition that it can occur in the manufacture of the product. The guidance lays out the conditions under which these risks can occur, and the steps that manufacturers should take to test for these potential impurities.

Under the agency's longstanding policies, manufacturers are required to test for impurities that may be introduced or develop during their manufacturing processes. We review that information in product applications, including requests to change the manufacturing process. We employ robust teams of organic chemists, as part of our newly established Office of Pharmaceutical Quality, to review applications and referenced information to look for steps – and manufacturing changes – where these risks could be introduced.

The FDA also inspects manufacturing facilities across the world, and in routine current good manufacturing practices inspections, we can review a manufacturer's records regarding impurity testing. However, the review of records depends on appropriate tests to detect the impurity. Tests are selected based on assessments of what impurities may develop based on the manufacturing process. In other words, it needs to be recognized that the risk of an impurity can occur in order to know that it should be tested for.

Recognizing these risks is based on a deep understanding of the chemistry involved in drug manufacturing, and the theoretical risk that an impurity could be a by-product of an essential step used in the manufacture of an active ingredient. When these impurities are identified, there are ways to re-engineer manufacturing processes to find pathways that don't create these by-products. Because it was not anticipated that NDMA would occur at these levels in the manufacturing of the valsartan API, manufacturers would not have been testing for it. They would not have records that help identify this issue during an inspection. So this particular risk would not have been identified on an inspection. As we develop a better understanding of the root cause of NDMA formation, and develop a way to detect NDMA in valsartan or other ARBs, we can ensure that appropriate testing is performed in the future.

Based on our analyses of the manufacturing processes, we are now testing all the products in the ARB class to determine if they contain NDMA. In some cases, the steps in the synthesis of other ARBs can have similarities to the synthesis of valsartan. These tests will continue until we identify all products that may contain NDMA in the ARB class, and they are no longer available in the U.S. And our robust investigation continues, as do our efforts to mitigate these risks and prevent them from recurring.

The FDA has also inspected ZHP in response to this problem and the agency may re-inspect ZHP and inspect other manufacturers of valsartan API in the future. The FDA is coordinating with companies to take swift action to remove any products found with unacceptable amounts of NDMA from the U.S. market.

The initial recall has expanded to now include five manufacturers and other companies who repackage those products under a different name. More products may need to be recalled. At the same time, the FDA is working to make certain that patients have access to the treatment that they need. Currently, more than half of all valsartan products on the market are being recalled. But prescribers can find a similar replacement product within the same class to substitute for patients who require this medication.

We are also working very closely with global regulatory agencies, including the European Medicines Agency. The task force the FDA formed exchanges information with regulatory counterparts around the world including inspection findings, laboratory test method and results, and our scientific assessment of the cause of this problem and its impact on patients. While not every manufacturing site produces drugs for all countries, we believe sharing this information is vital to advancing our ongoing investigation. It enables us to address emerging issues quickly in a way that benefits U.S. patients. This includes monitoring actions other regulators are taking as part of their investigations. For example, international regulators have identified another API manufacturer, Zhejiang Tianyu Pharmaceutical Co., with NDMA in its valsartan API. But the FDA has confirmed that no valsartan products in the U.S. market use this API.

The FDA will continue to work closely with providers and patients to address health care needs.

The news of the recall caused a significant public response. Consumers were rightly concerned. CDER has a skilled group of pharmacists and nurses who manage a toll-free number (/about-fda/about-center-drug-evaluation-and-research/cder-division-drug-information) (855-543-3784) and answer email inquiries (druginfo@fda.hhs.gov (mailto:druginfo@fda.hhs.gov)) from the public. Since the first news of a recall, the FDA has received more than 6,000 inquiries from patients, physicians, nurses, pharmacists and academicians. We take these inquiries very seriously, and we strive to answer all of them. The public wants to know how to get safe valsartan, what to tell their pharmacists, if they should stop taking their medications and how to calculate their risk for cancer if they have been taking affected valsartan for several years. It was these questions, in part, that prompted the FDA to conduct its analysis (/drugs/drug-safety-and-availability/fda-updates-valsartan-recalls) of the risk that NDMA posed.

As we develop a better understanding of the manufacturing process conditions that ZHP used that can cause the impurity, we will use that knowledge to inform assessments of product applications being submitted and currently reviewed by the FDA. We will disseminate that information to manufacturers of all drugs and to the scientific community and re-evaluate our existing guidance to manufacturers. In addition, the test method we developed for identifying NDMA helps us to prioritize assessments and inspections of manufacturing sites. The information we gather throughout this investigation will give us a better understanding of the manufacturing processes and will strengthen our efforts to keep the U.S. drug supply safe for patients.

In addition to our ongoing investigation, we will continue to update our website (/drugs/drug-safety-and-availability/fda-updates-valsartan-recalls), detailing lists of all recalled and non-recalled valsartan products as well as advice for patients and prescribers. We will also disclose our test results. This is a serious matter that is being managed closely by the FDA's leadership. As described above,we have a robust effort underway to evaluate these risks, led by a team of some of our most experienced scientists and clinicians. As we continue to investigate this episode, and develop new information, we will update the public regularly. We are committed to identifying the root causes of this impurity being found in valsartan, and taking steps to reduce the risk that similar episodes occur in the future.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

Related Information

FDA updates on valsartan recalls (/drugs/drug-safety-and-availability/fda-updates-valsartan-recalls)

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Inquiries

Media:

Jeremy Kahn (mailto:jeremy.kahn@fda.hhs.gov)

301-796-8671

Consumer:

888-INFO-FDA

More Press Announcements (/news-events/newsroom/press-announcements)

Exhibit 25

U.S. FOOD & DRUG ADMINISTRATION

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Via UPS
Return Receipt Requested

Warning Letter: 320-19-04

November 29, 2018

Mr. Jun Du
Executive Vice President
Zhejiang Huahai Pharmaceutical Co., Ltd.
Coastal Industrial Zone, Chuannan No. 1 Branch No. 9
Donghai Fifth Avenue, Linhai, Taizhou Zhejiang 317016
CHINA

Dear Mr. Du:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Zhejiang Huahai Pharmaceutical Co., Ltd., located at Coastal Industrial Zone, Chuannan No. 1 Branch No. 9, Donghai Fifth Avenue, Linhai, Taizhou Zhejiang, from July 23 to August 3, 2018.

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your August 26, 2018, response in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators observed specific deviations including, but not limited to, the following.

1. **Failure of your quality unit to ensure that quality-related complaints are investigated and resolved.**

Valsartan API

Your firm received a complaint from a customer on June 6, 2018, after an unknown peak was detected during residual solvents testing for valsartan API manufactured at your facility. The unknown peak was identified as the probable human carcinogen N-nitrosodimethylamine (NDMA). Your investigation (DC_E-18001) determined that the presence of NDMA was caused by the convergence of three process-related factors, one factor being the use of the solvent dimethylformamide (DMF). Your investigation concluded that only one valsartan manufacturing

process (referred to as the $ZnCl_2$ process in your investigation) was impacted by the presence of NDMA.

However, FDA analyses of samples of your API, and finished drug product manufactured with your API, identified NDMA in multiple batches manufactured with a different process, namely the triethylamine process, which did not use the solvent DMF. These data demonstrate that your investigation was inadequate and failed to resolve the control and presence of NDMA in valsartan API distributed to customers. Your investigation also failed:

- To include other factors that may have contributed to the presence of NDMA. For example, your investigation lacked a comprehensive evaluation of all raw materials used during manufacturing, including potable water.

- To assess factors that could put your API at risk for NDMA cross-contamination, including batch blending, solvent recovery and re-use, shared production lines, and cleaning procedures.

- To evaluate the potential for other mutagenic impurities to form in your products.

Our investigators also noted other examples of your firm's inadequate investigation of unknown peaks observed in chromatograms. For example, valsartan intermediates (C20213-17-339 and C20213-17-340) failed testing for an unknown impurity (specification $\leq 0.5\%$) with results of 0.56% for both batches. Your action plan indicated that the impurity would be identified as part of the investigation; however, you failed to do this. In addition, no root cause was determined for the presence of the unknown impurity. You stated that you reprocessed the batches and released them for further production.

Your response states that NDMA was difficult to detect. However, if you had investigated further, you may have found indicators in your residual solvent chromatograms alerting you to the presence of NDMA. For example, you told our investigators you were aware of a peak that eluted after the toluene peak in valsartan API residual solvent chromatograms where the presence of NDMA was suspected to elute. At the time of testing, you considered this unidentified peak to be noise and investigated no further. Additionally, residual solvent chromatograms for valsartan API validation batches manufactured using your $ZnCl_2$ process, with DMF in 2012 (C5355-12-001, C5355-12-002, and C5355-12-003) show at least one unidentified peak eluting after the toluene peak in the area where the presence of NDMA was suspected to elute.

Your response also states that you were not the only firm to identify NDMA in valsartan API. In your case, FDA analyses of samples identified amounts of NDMA in valsartan API manufactured at your firm that were significantly higher than the NDMA levels in valsartan API manufactured by other firms. FDA has grave concerns about the potential presence of mutagenic impurities in all intermediates and API manufactured at your facility, both because of the data indicating the presence of impurities in API manufactured by multiple processes, and because of the significant inadequacies in your investigation.

In response to this letter:

- Submit risk assessments for all APIs and intermediates manufactured at your facility for the potential presence of mutagenic impurities.

- Provide an update on investigations and CAPA plans initiated to address the presence of NDMA and other potential mutagenic impurities in all APIs manufactured at your firm.

- Provide a thorough, independent assessment of your overall system for investigating deviations, discrepancies, out-of-specification (OOS) results, complaints, and other failures. In addition, provide a retrospective review of all distributed batches within expiry to determine if your firm released batches that did not conform to established specifications or appropriate manufacturing standards.

- Provide test results for all angiotensin II receptor blockers (ARBs) and intermediates for the presence of NDMA, N-Nitrosodiethylamine (NDEA), and other potentially mutagenic impurities.

Levetiracetam API

Your firm received a customer complaint on September 13, 2016, concerning levetiracetam API batches (C5152-16-243 and C5152-16-254) that exceeded the specification for ethyl carbamate ($\leq$ 0.24 ppm). Ethyl carbamate has been classified as a probable human carcinogen. Your customer's test results conflicted with your ethyl carbamate test results, which showed the two batches meeting the specification upon release. Your complaint investigation (CC-16008) identified no clear laboratory error, and no anomalies were detected during the production of the batches. Your investigation failed to evaluate other levetiracetam API batches to determine if the presence of excess ethyl carbamate was an adverse trend. For example, levetiracetam batches C5152-16-244, C5152-16-250, and C5152-16-251 were OOS for ethyl carbamate because of production errors; however, they were not discussed in your complaint investigation.

Your response states that levetiracetam API batches C5152-16-243 and C5152-16-254 were returned, reprocessed, and released to customers in non-U.S. markets.

Your response also states that in August 2017 you implemented a new ethyl carbamate test method that uses a triple quadrupole LC-MS/MS method, to replace the single quadrupole LC-MS method that was prone to erroneous OOS results. You failed to verify the reliability of the ethyl carbamate results for all levetiracetam API batches (including levetiracetam batch C5152-16-254) originally released using your single quadrupole LC-MS method, which you indicated was inferior to your updated method.

In response to this letter, provide:

- A risk assessment for all levetiracetam API batches manufactured within expiry.

- A revised complaint handling procedure and details of any further controls your facility has implemented to ensure that all complaints are adequately documented and thoroughly investigated.

- Procedures for accepting and reprocessing returned drugs.

- Results of ethyl carbamate testing of all levetiracetam API batches released to the U.S. market using your updated triple quadrupole LC-MS/MS ethyl carbamate test method.

2. Failure to evaluate the potential effect that changes in the manufacturing process may have on the quality of your API.

In November 2011 you approved a valsartan API process change (PCRC - 11025) that included the use of the solvent DMF. Your intention was to improve the manufacturing process, increase product yield, and lower production costs. However, you failed to adequately assess the potential formation of mutagenic impurities when you implemented the new process. Specifically, you did not consider the potential for mutagenic or other toxic impurities to form from DMF degradants, including the primary DMF degradant, dimethylamine. According to your ongoing investigation, dimethylamine is required for the probable human carcinogen NDMA to form during the valsartan API manufacturing process. NDMA was identified in valsartan API manufactured at your facility.

You also failed to evaluate the need for additional analytical methods to ensure that unanticipated impurities were appropriately detected and controlled in your valsartan API before you approved the process change. You are responsible for developing and using suitable methods to detect impurities when developing, and making changes to, your manufacturing processes. If new or higher levels of impurities are detected, you should fully evaluate the impurities and take action to ensure the drug is safe for patients.

Your response states that predicting NDMA formation during the valsartan manufacturing process required an extra dimension over current industry practice, and that that your process development study was adequate. We disagree. We remind you that common industry practice may not always be consistent with CGMP requirements and that you are responsible for the quality of drugs you produce.

Your response does not describe sufficient corrective actions to ensure that your firm has adequate change management procedures in place: (1) to thoroughly evaluate your API manufacturing processes, including changes to those processes; and (2) to detect any unsafe impurities, including potentially mutagenic impurities. For FDA's current thinking on control of potentially mutagenic impurities, see FDA's guidance document *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk* for approaches that FDA considers appropriate for evaluating mutagenic impurities, at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf.

In response to this letter, provide:

- Detailed revised change management procedures describing how your firm will assess and control all impurities, including mutagenic impurities, in API and intermediates manufactured at your facility.

- Detailed procedures describing how your firm establishes impurity profiles for products manufactured at your firm. These procedures should contain instructions for comparing at appropriate intervals against the impurity profile in the regulatory submission, or for comparing against historical data, to detect changes to the API resulting from modifications in raw materials, equipment operating parameters, or the production process.

- A retrospective analysis of other API and intermediates manufactured at your firm to determine if they were adequately evaluated for anticipated and unanticipated impurities, including potentially mutagenic impurities.

CGMP consultant recommended

Based upon the nature of the deviations we identified at your firm, we strongly recommend engaging a consultant qualified to evaluate your operations and assist your firm in meeting CGMP requirements. Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

Quality Systems Guidance

Your firm's quality systems are inadequate. For guidance on establishing and following CGMP compliant quality systems, see FDA's guidances: *Q8(R2) Pharmaceutical Development*, at https://www.fda.gov/downloads/drugs/guidances/ucm073507.pdf; *Q9 Quality Risk Management*, at https://www.fda.gov/downloads/Drugs/Guidances/ucm073511.pdf; and *Q10 Pharmaceutical Quality System*, at https://www.fda.gov/downloads/drugs/guidances/ucm073517.pdf.

Additional API CGMP guidance

FDA considers the expectations outlined in ICH Q7 in determining whether API are manufactured in conformance with CGMP. See FDA's guidance document *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* for guidance regarding CGMP for the manufacture of API, at https://www.fda.gov/downloads/Drugs/.../Guidances/ucm073497.pdf.

Conclusion

Deviations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these deviations, for determining the causes, for preventing their recurrence, and for preventing other deviations.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) and allows FDA to consider, as soon as possible, what

actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

FDA placed your firm on Import Alert 66-40 on September 28, 2018.

Until you correct all deviations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Failure to correct these deviations may also result in FDA continuing to refuse admission of articles manufactured at Zhejiang Huahai Pharmaceutical Co., Ltd., located at Coastal Industrial Zone, Chuannan No. 1 Branch No. 9, Donghai Fifth Avenue, Linhai, Taizhou Zhejiang, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your deviations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov or mail your reply to:

Rory K. Geyer
Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4235
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3003885745.

Sincerely,

Francis Godwin
Acting Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

Exhibit 26

Notice on the Results of the Report of the Preliminary Investigation on the Formation of Unknown Impurities Resulting from the Sodium Azide Quenching in Crude Irbesartan

Jinsheng LIN

To: Jucai GE, Tianpei HUANG, Wangwei CHEN, Wenquan ZHU, Wenbin CHEN, Mr. Li, Peng DONG, Lihong LIN, Yanfeng LIU, Peng WANG, Wenling ZHANG 07/27/2017 Detailed Information

Valsartan Impurity K.pdf (846 KB)

Ms. Ge:

According to the results of our telephone communication with the Technology Department of Chuannan Plant 1 today, due to the incomplete quenching of sodium azide caused by the separate treatment of irbesartan sodium azide wastewater, there is the frequent occurrence of muffled explosion in the production process, so the Technology Department carried out the technical improvement by which the sodium azide quenching takes place in the unstratified step in the crude irbesartan process. However, after the improvement, there is an unknown impurity of about 0.544% at 26 minutes in the crude irbesartan, and it is the largest impurity in the irbesartan crude product.

[redacted]

Min Li
ZHP-296
4/20/2021

Through the secondary mass spectrometry analysis, it can be inferred that the extra NO substituent is in the cyclic compound fragment, and it is very likely that it is an N-NO compound; it is similar to the N-nitrosodimethylamine that occurs in valsartan when quenched with sodium nitrite, and its structure is very toxic. Its possible formation route is shown as follows:

In order to further verify the structure of the impurity and its formation mechanism, we plan to simulate the quenching conditions and use the finished Irbesartan product to react with $NaNO_2$ and HCl to monitor the impurity produced by the reaction, and then separate it for NMR for final structural verification, while simultaneously carrying out the confirmation of the impurity by multi-stage MS.

If it is confirmed as the above speculated structure, then its toxicity will be very strong, and there will be an extremely high GMP risk. This is a common problem in the production and synthesis of sartan APIs. It is recommended to improve other quenching processes (such as NaClO) along with the optimization of the valsartan sodium azide quenching process.

I've also attached a patent of a 2013 sodium azide NaClO quenching method by Zhejiang Second Pharma Co., Ltd. they proposed that the use of $NaNO_2$ quenching will result in the formation of N-NO impurities. At the same time, they used ZHP's crude Valsartan in their LC-MS test and detected this impurity. This indicates that other companies have paid attention to the quality problem very early on. So leaders please pay attention to this issue.

Jinsheng LIN

CEMAT

2017/07/27

Exhibit 27

2013 WL 1558690
NOT FOR PUBLICATION
United States District Court, D. New Jersey.

In re FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION.
Bernadette Glynn and Richard Glynn, Plaintiffs,
v.
Merck Sharp & Dohme Corp, Defendant.

Civil Action Nos. 11–5304, 08–08.
|
April 10, 2013.

Attorneys and Law Firms

Donald A. Ecklund, James E. Cecchi, Carella Byrne Cecchi Olstein Brody & Agnello, P.C., Roseland, NJ, Christopher A. Seeger, David R. Buchanan, Seeger Weiss, LLP, Newark, NJ, Edward Braniff, Weitz & Luxenberg, New York, NY, for Plaintiffs.

David J. Heubeck, Venable LLP, Baltimore, MD, Karen A. Confoy, Fox Rothschild LLP, PC, Lawrenceville, NJ, for Defendant.

OPINION

PISANO, District Judge.

***1** Plaintiffs Bernadette Glynn and Richard Glynn ("Plaintiffs") bring this lawsuit against Defendant Merck, Sharp, & Dohme Corp. ("Defendant"), which manufactures Fosamax, a drug approved by the United States Food and Drug Administration ("FDA") for the treatment and prevention of osteoporosis. This matter is part of the multi-district litigation concerning Fosamax and involves allegations that Fosamax causes atypical femur fractures ("AFFs [1]") and that it caused Plaintiff Mrs. Glynn ("Mrs.Glynn")'s femur fracture. Presently before the Court is Defendant's Omnibus *Daubert* Motion to exclude the expert testimony of Dr. Charles N. Cornell ("Dr.Cornell"), Dr. Michael J. Klein ("Dr.Klein"), Dr. David Madigan ("Dr.Madigan"), and Dr. Cheryl Blume ("Dr.Blume") as well as a motion to exclude the causation testimony of the treating physicians—Dr. Robert Busch ("Dr.Busch"), Dr. Robert Lindsay ("Dr.Lindsay"), Dr. Frederick Fletcher ("Dr.Fletcher"), and Dr. Britton Limes ("Dr.Limes") [docket # 28]. This Court heard oral argument on February 21, 2013 and April 2, 2013. For the reasons outlined below, the Motion is denied as to Drs. Cornell, Klein, Madigan, and Blume. The treating physicians' causation testimony will not be excluded if their opinions are based on their treatment and care of Mrs. Glynn.

I. DISCUSSION

Federal Rule of Evidence 702 provides that a witness

> qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if:
>
> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
>
> (b) the testimony is based on sufficient facts or data;
>
> (c) the testimony is the product of reliable principles and methods; and
>
> (d) the expert has reliably applied the principles and methods to the facts of the case.

This Rule requires the proponent of expert testimony to show the "requisite 'qualifications, reliability, and fit' " or in other words, that "(1) the witness is qualified as an expert in a particular field; (2) the methodology applied by the witness is sufficiently reliable; and (3) the witness's testimony 'fits' the facts of the case in dispute—that is, the proffered testimony would assist the trier of fact." *Jones v. Synthes USA Sales, LLC,* 2010 WL 3311840, *4 (D.N.J. Aug.19, 2010); *see also* *McNamara v. Kmart Corp.,* 380 Fed. Appx. 148, 151 (3d Cir.2010); *Meadows v. Anchor Longwall & Rebuild, Inc.,* 306 Fed. Appx. 781, 788 (3d Cir.2009); *Pineda v. Ford Motor Co.,* 520 F.3d 237, 244 (3d Cir.2008); *Schneider ex rel. Estate of Schneider v. Fried,* 320 F.3d 396, 404 (3d Cir.2003).

First, the expert must be qualified; this requirement is interpreted liberally and "a broad range of knowledge, skills, and training qualify an expert as such." *In re Paoli R.R. Yard PCB Litigation,* 35 F.3d 717, 741 (3d Cir.1994).

***2** Second, "an expert's testimony is admissible so long as the process or technique the expert used in formulating

the opinion is reliable." *Id.* at 742. An expert's opinion is reliable if it is "based on 'good grounds,' i.e., if it is based on the methods and procedures of science." *Id.* at 744. This inquiry requires a court to examine the "scientific validity and thus the evidentiary relevance and reliability [ ] of the principles that underlie a proposed submission" and to focus "solely on principles and methodology, not on the conclusions ... [the expert] generate[s]." *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 594–95, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993). In *Daubert,* the Supreme Court outlined several factors that a court may take into consideration in determining reliability, including whether the hypothesis can be tested, whether the methodology "has been subjected to peer review and publication," the methodology's rate of error, "the existence and maintenance of standards controlling the technique's operation," and whether there is general acceptance in the scientific community. *Id.* at 593–94. The proponent of the expert testimony must demonstrate that the opinions are reliable by a preponderance of the evidence. *In re Paoli,* 35 F.3d at 744.

Third, expert testimony "must fit the issues in the case" or in other words, "be relevant for the purposes of the case and must assist the trier of fact." *Schneider,* 320 F.3d at 404. The Court must determine "whether [the] expert testimony proffered ... is sufficiently tied to the facts of the case that it will aid the jury in resolving a factual dispute." *United States v. Schiff,* 602 F.3d 152, 173 (3d Cir.2010). This standard "is not that high" but "higher than bare relevance." *In re Paoli,* 35 F.3d at 745.

The Court's role, at a *Daubert* hearing, is to act "as a gatekeeper, preventing opinion testimony that does not meet the requirements of qualification, reliability and fit from reaching the jury." *Schneider,* 320 F.3d at 404. In keeping with its gatekeeping role, this Court will apply the *Daubert* analysis to each expert.

A. Dr. Cornell

Plaintiffs offer Dr. Cornell, an orthopedist, as an expert in causation, to establish that Fosamax causes AFFs and Mrs. Glynn's Fosamax use caused her AFF.

1. Dr. Cornell Is Qualified as an Expert

Dr. Cornell is currently a Professor of Clinical Orthopedic Surgery at Weill Cornell College of Medicine and has been the Richard Laskin Chair in Orthopedic Surgery since 2011 [docket # 102, Ex. 8, Dr. Cornell's Report ("Cornell Report") at 2]. In addition, Dr. Cornell is an attending orthopedic surgeon at the Hospital for Special Surgery in New York City and currently serves as the hospital's Director of the Department of Orthopedic Surgery. *Id.* He is a "specialist in orthopedic trauma ... and metabolic bone disease," which includes osteoporosis and osteopenia [docket # 102, Ex. 10, Dr. Cornell's Deposition ("Cornell Dep.") at 69:13–16; 71:14–17]. About 80% of all the fractures Dr. Cornell treats surgically are fractures "as a consequence of osteoporosis or osteopenia." *Id.* at 72:6–21. He has treated two patients with atypical fractures related to bisphosphonate use. Cornell Report at 3. Moreover, he has "participated in a study to determine a management strategy for the treatment of symptomatic bisphosphonate-associated incomplete atypical femoral fractures, which was peer reviewed and published in the Hospital for Special Surgery Journal." *Id.* Although Defendant argues that Dr. Cornell is not qualified because he is not trained in epidemiology and is unfamiliar with "the most basic epidemiological terms and concepts" (Db13 [2]), Dr. Cornell does not have to possess a particular subspecialty—epidemiology—to testify as an expert. *See Schneider,* 320 F.3d at 406–07 (determining that testimony was improperly excluded because an individual "was not an expert in the sub-specialty about which he opined"); *Holbrook v. Lykes Bros. S.S. Co., Inc.*, 80 F.3d 777, 783 (3d Cir.1996) (declaring that the lower court erred by requiring the expert to have a particular specialization and "exact background"); *see also Keller v. Feasterville Family Health Care Ctr.,* 557 F.Supp.2d 671, 675 (E.D.Pa.2008) (recognizing that expert testimony cannot be excluded because "the expert is without the appropriate specialization" and that "[a] certain degree of background is not required"). Because Dr. Cornell has the academic background and professional experience with osteoporosis, osteopenia, and fractures associated with those diseases, he is qualified to testify as an expert in this case. *See Schneider,* 320 F.3d at 407.

2. Dr. Cornell's Methodology Is Sufficiently Reliable

***3** Dr. Cornell formed his opinion using the Bradford Hill criteria, which are "nine factors widely used in the

scientific community to assess general causation." *Gannon v. United Sates,* 292 Fed. Appx. 170, 173 (3d Cir.2008); Cornell Dep. at 329:5–8. General causation is when "an observed association between a chemical and a disease is causal." *Magistrini v. One Hour Martinizing Dry Cleaning,* 180 F.Supp.2d 584, 592 (D.N.J.2002), *aff'd,* 68 Fed. Appx. 356 (3d Cir.2003). The nine Bradford Hill factors are: "1. Temporal Relationship, 2. Strength of the association, 3. Dose-response relationship, 4. Replication of the findings, 5. Biological plausibility (coherence with existing knowledge), 6. Consideration of alternative explanations, 7. Cessation of exposure, 8. Specificity of the association, and 9. Consistency with other knowledge." FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, at 599–600 (3d ed.2011), *available at* http://www.fjc.gov/public/pd f.nsf/lookup/SciMan3D01.pdf/$file/SciMan3D01.pdf; *see also Gannon,* 292 Fed. Appx. at 173 n. 1; *In re Avandia Mktg., Sales Practices & Products Liab. Litig.,* 2011 WL 13576, *3 (E.D.Pa. Jan.4, 2011); *Magistrini,* 180 F.Supp.2d at 592–93. "[O]ne or more of the factors may be absent even where a causal relationship exists and ... no factor is a sine qua non of causation. *Magistrini,* 180 F.Supp.2d at 593 n. 9.

Dr. Cornell used the Bradford Hill criteria to form an opinion on whether Fosamax causes AFFs. Cornell Dep. at 331:4–8; Cornell Report at 4. In applying the nine Bradford Hill factors, he reviewed Plaintiff's medical records from 1996 to present, the office notes and depositions of her treating physicians, and "past and current medical literature on the topics of osteopenia, osteoporosis and their prevention and treatment with bisphosphonate drugs including alendronate," particularly publications concerning the FIT and FLEX studies and that described the appearance of AFFs. Cornell Report at 3, 4–5. He "review[ed] the original trials, the randomized trials, that led to the approval of Fosamax for the treatment of osteoporosis, and then wanted to review many of the case reports, the case series, the summed analysis, and some of the review papers that took all of this information and put it into a more readily digestible form." Cornell Dep. at 56:13–23. Dr. Cornell attempted to "present a balanced analysis" and pointed out studies on both sides of the issue. *Id.* at 58:5–16. He concluded that Fosamax can cause AFFs and "Fosamax use was a substantial contributing factor to Mrs. Glynn's femur fracture." Cornell Report at 4. The methodology Dr. Cornell used is sufficiently reliable because the Bradford Hill criteria are "broadly accepted" in the scientific community "for evaluating causation," *Gannon,* 292 Fed. Appx. at 173 n. 1, and "are so well established in epidemiological research," *In re Avandia Mktg. ., Sales Practices & Products Liab. Litig.,* 2011 WL 13576, at *3.

***4** Defendant, however, argues that Plaintiffs do not explain the scientific methodology used by Dr. Cornell or show that his methodology is sufficiently reliable. Instead, Defendant asserts that Dr. Cornell's "weight-of-the-evidence" methodology just lists some studies, only some of which support causation, and concludes that the weight of the evidence shows that Fosamax causes AFFs. Defendant explains that this method is inadequate because Dr. Cornell does not discuss how these studies establish causation or why certain studies outweigh others that do not find causation. Additionally, Defendant points out that Dr. Cornell has not done an evaluation of possible biases or confounding factors found in the studies. Because Dr. Cornell does not show that his methodology is sufficiently reliable to show general causation, Defendant argues that he cannot establish specific causation—that Mrs. Glynn's Fosamax use caused her AFF. Defendant explains that the Bradford Hill criteria do not apply to specific causation, and Dr. Cornell's differential diagnosis was unreliable because he did not rule out the possibility that other things could have caused Mrs. Glynn's fracture.

Defendant is free to address these issues on cross-examination, but Defendant's concerns do not prohibit Dr. Cornell from testifying as an expert because he is qualified and the methodology he used is sufficiently reliable. *See Milward v. Acuity Specialty Products Group, Inc.,* 639 F.3d 11, 15 (1st Cir.2011), *cert. denied,* —— U.S. ——, 132 S.Ct. 1002, 181 L.Ed.2d 734 (2012) (stating *"Daubert* does not require that a party who proffers expert testimony carry the burden of proving to the judge that the expert's assessment of the situation is correct"; instead, the "proponent of the evidence must show only that 'the expert's conclusion has been arrived at in a scientifically sound and methodologically reliable fashion.' ").

Regarding Dr. Cornell's specific causation opinion that Fosamax caused Mrs. Glynn's femur fracture, he applied the differential diagnosis method, which is "a technique that involves assessing causation with respect to a particular individual." *Kannankeril v. Terminix Int'l, Inc.,* 128 F.3d 802, 807 (3d Cir.1997). It "is a process by which a physician rules out alternative causes through review of a patient's medical histories and records, physical examination of the patient, laboratory testing, study of

relevant medical literature, and other techniques." *In re Diet Drugs (Phentermine/Fenfluramine/Dexfenfluramine) Products Liab. Litig.,* 890 F.Supp.2d 552, 561 (E.D.Pa.2012). The "technique is generally accepted in the medical community." *Id.*

Here, Dr. Cornell applied the differential diagnosis method by examining Mrs. Glynn's past medical history and conducting his own examination of her on September 26, 2012, after which he concluded that "[t]o a reasonable degree of medical certainty, Mrs. Glynn suffered a nontraumatic [AFF] in the setting of seven years of full dose Fosamax and alendronate therapy." Cornell Report at 34–36. Dr. Cornell reviewed radiographs taken on April 17, 2009 to evaluate the fracture and reviewed follow-up X-rays, hospital records, rehabilitation records, orthopedics records, prescription records from pharmacies, and deposition transcripts, among other things, in forming his opinion [docket # 109, Ex. 78, Appendix B to Cornell Report]. He ruled out possible alternative causes of Mrs. Glynn's AFF. Cornell Report at 38–40, 42–43, 45–46. Dr. Cornell did not have to "rule out every possible alternative cause of" Mrs. Glynn's AFF; instead, only "[o]bvious alternative causes need to be ruled out." *Heller v. Shaw Indus., Inc.,* 167 F.3d 146, 156 (3d Cir.1999). Thus, Dr. Cornell applied the differential diagnosis method in arriving at his conclusion that Mrs. Glynn's Fosamax use was a substantial contributing factor to her AFF.

***5** Therefore, the methodology used by Dr. Cornell in arriving at both his general and specific causation opinions is sufficiently reliable. Both the Bradford Hill criteria and differential diagnosis are widely used and accepted in the scientific community to arrive at causation opinions.

3. Dr. Cornell's Testimony Fits the Facts of the Case

Finally, Dr. Cornell's testimony fits the facts of the dispute and will assist the trier of fact because Plaintiffs seek to show that Mrs. Glynn's AFF was caused by her Fosamax use and Dr. Cornell not only opines that AFFs are caused by long term bisphosphonate use, like Fosamax, but also that Mrs. Glynn's Fosamax use was a "substantial contributing factor to her" AFF. *See* Cornell Report at p. 22, 47. Consequently, Dr. Cornell's proffered testimony will assist the trier of fact in determining whether Fosamax caused Mrs. Glynn's AFF.

Because Dr. Cornell is qualified, used a methodology that is sufficiently reliable, and his opinion fits the facts of a case, his expert testimony is admissible under *Daubert.*

B. Dr. Klein

Plaintiffs asked Dr. Klein, a pathologist, to offer his opinion on whether Fosamax use causes AFFs and the "mechanism by which those fractures are precipitated" [docket # 103, Ex. 11, Dr. Klein's Report ("Klein Report") at 2].

1. Dr. Klein Is Qualified as an Expert

Dr. Klein is currently the Director of Pathology and Laboratory Medicine at the Hospital for Special Surgery where he has "direct clinical responsibilities for patients ...." *Id.* at 3–4. He also has "direct clinical responsibilities ... as a consultant at Memorial Sloan–Kettering Cancer Center, and as an outside counsel for leading pathology laboratories at major hospitals and institutions around the country." *Id.* at 4. Dr. Klein has reviewed the pathology for at least four patients with AFFs [docket # 105, Ex. 37, Dr. Klein's Deposition ("Klein Dep.") at 41:4–12]. Dr. Klein is currently a Professor of Pathology and Laboratory Medicine at Weill Cornell Medical College. Klein Report at 3. He is involved with several publications, including as the lead author and editor of *Non-neoplastic Diseases of Bones and Joints,* the only peer-reviewed, comprehensive textbook on the issue, and as a member of the editorial boards of *Human Pathology, Skeletal Radiology, Advances in Anatomical Pathology,* and *HSS Journal. Id.* Dr. Klein is the Consultant Editor of Research for *The Journal of Bone and Joint Surgery (American)* and has authored or co-authored more than 180 articles, most of which relate to bone pathology. *Id.* Therefore, Dr. Klein possesses "a broad range of knowledge, skills, and training" to qualify him as an expert in pathology. *In re Paoli,* 35 F.3d at 741.

2. Dr. Klein's Methodology Is Sufficiently Reliable

Like Dr. Cornell, Dr. Klein used the Bradford Hill criteria to form his opinion. Klein Report at 2. As discussed above, the Bradford Hill methodology is sufficiently reliable because it is "widely used in the scientific community to assess general causation." *Gannon,* 292 Fed. Appx. at 173. In applying the nine Bradford Hill criteria, Dr. Klein reviewed human and animal studies and studies performed by Defendant to form his opinion. *See* Klein Report at19–38. The studies revealed a strong association between bisphosphonates, like Fosamax, and microdamage in the bones as well as decreased bone toughness. *See id.* at 20, 25–30, 32. In addition, Dr. Klein noted a strong association between delayed fracture healing, due to altered bone quality, in patients and animals taking bisphosphonates. *Id.* at 23–24, 29. These findings

were replicated in several studies discussed in Dr. Klein's report. Moreover, Dr. Klein cited one study which recognized the *"duration*-dependent, as well as dose-dependent, effect bisphosphonates have on the skeleton." *Id.* at 27. Another study mentioned in Dr. Klein's report noted that the "cessation of bisphosphonate treatment may be prudent for women on therapy who sustain a nonvertebral fracture." *Id.* at 30. Thus, Dr. Klein applied the Bradford Hill criteria, including the strength of association, replication of findings, dose-response relationship, and cessation of exposure factors.

***6** Based on his review of the studies, Dr. Klein concluded that "alendronate significantly alters the cellular properties of bisphosphonate-treated bone." *Id.* at 38. AFFs are not

> attributed to low bone mass or osteoporosis alone, indicative of bone that has fundamentally compromised bone microstructure. Unless a damaging force exerts tension across the entire cortex, the laws of physics and biomechanics as applied to bone further support the conclusion that bone quality and microstructure must be fundamentally compromised for a transverse fracture in a hollow cylinder[, like the femur,] to follow.
>
> [*Id.*]

Thus, Dr. Klein opined that there is a causal relationship between Fosamax and AFFs. *Id.* at 2. He used a sufficiently reliable methodology, the Bradford Hill criteria, in forming this opinion.

Defendant, however, argues that the Bradford Hill criteria apply to epidemiology studies, which Dr. Klein's report does not discuss. Defendant contends that Dr. Klein has not provided support for the proposition that a general causation conclusion can be established using the Bradford Hill criteria and human or animal biopsy data. In addition, Defendant asserts that if Dr. Klein discussed epidemiology studies in his report, he did not demonstrate that he is qualified to interpret that evidence because he has no expertise in epidemiology and does not understand the most basic epidemiology terms. Moreover, Defendant points out that Dr. Klein conceded that the mechanism regarding how bisphosphonates cause AFFs has not been established and that the theories Dr. Klein uses to support his conclusion about mechanism—microdamage, decrease in tissue heterogeneity, bone brittleness, and delayed healing—have not been proved with human data.

Yet, Dr. Klein has properly applied the Bradford Hill criteria to epidemiological studies. Epidemiological studies include randomized trials in which one group is exposed to an agent, such as Fosamax, and another group is not, and the effect of the agent or lack thereof is observed. FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE at 555–56. Here, Dr. Klein examined randomized trials, such as Dempster et al., Boskey et al., and Donnelly et al.; in each of these studies, some women were given alendronate or another bisphosphonate and others were not. Klein Report at 20–21. Moreover, the Federal Judicial Center's Reference Manual on Scientific Evidence states that "toxicology models based on live animal studies ... may be used to determine toxicity in humans" in addition to observational epidemiology. FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, at 563.

For his testimony to be admissible, Dr. Klein is not required to show that the mechanism has been definitely established. Instead, he just needs to show that the methodology he used to arrive at his opinion is sufficiently reliable. *See* *Milward,* 639 F.3d at 15 (stating *"Daubert* does not require that a party who proffers expert testimony carry the burden of proving to the judge that the expert's assessment of the situation is correct"; instead, the "proponent of the evidence must show only that 'the expert's conclusion has been arrived at in a scientifically sound and methodologically reliable fashion.' "). Dr. Klein arrived at his opinion on the mechanism by examining several studies and using a scientific method that is sufficiently reliable.

3. Dr. Klein's Testimony Fits the Facts of the Case

***7** Lastly, Dr. Klein's testimony fits the facts of the dispute and will assist the trier of fact. *See Jones,* 2010 WL 3311840, at *4. Through Dr. Klein's testimony, Plaintiffs seek to show that Fosamax causes AFFs and the mechanism by which this happens. *See* Klein Report at 2. Dr. Klein opines that Fosamax causes AFFs and discusses several ways this happens—microdamage, abnormal osteoclasts, altered bone quality, and delayed fracture healing. Thus, Dr. Klein's testimony will assist the trier of fact in determining whether Fosamax causes AFFs, the ways in which this happens, and ultimately, his testimony will aid the jury in deciding whether Mrs. Glynn's Fosamax use caused her AFF.

C. Dr. Madigan

Plaintiffs asked Dr. Madigan, a statistician, to give his opinion regarding "whether a signal of problematic oversuppression

of bone turnover and associated [AFF] ... existed for Fosamax, using industry standard pharmacovigilance techniques and data sources, and the adverse event terms selected by Merck to internally evaluate the same" and "assess the strength of that signal, if any, in comparison to the signal, if any, for such events in other products indicated for the prevention and treatment of osteoporosis" [docket # 33, Ex. 30, Dr. Madigan's Report ("Madigan Report") at ¶ 5].

1. Dr. Madigan Is Qualified as an Expert

Dr. Madigan is Professor and Chair of Statistics at Columbia University. *Id.* at ¶ 1. He is an elected Fellow of the Institute of Mathematical Statistics and the American Statistical Association, and from 1995 to 2005 was the 36th most cited mathematician worldwide. *Id.* In 2010, he completed a term as Editor of the journal *Statistical Science. Id.* Dr. Madigan has consulted for companies such as Novartis, Pfizer, and Sanofi–Aventis on several issues, "many related to drug safety." *Id.* at ¶ 2. He has statistical experience with clinical trials and has published more than 100 technical papers on many topics, including pharmacovigilance[3]. *Id.*

Within the last few years, drug safety "with a focus on the development and application of statistical methods for pharmacovigilance" has been "one of [Dr. Madigan's] significant research interests ...." *Id.* at ¶ 3. He has published work in several journals, including *Drug Safety, Pharmacoepidemiology and Drug Safety,* and *Epidemiology. Id.* Dr. Madigan is an investigator in the Mini–Sentinel project, which is "a pilot project sponsored by the FDA to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products." *Id.* He is the "methods lead for the Observational Medical Outcomes Partnership, a public-private partnership between the FDA and the pharmaceutical industry, which addresses "research methods that are feasible and useful to analyze existing healthcare databases to identify and evaluate safety and benefit issues of drugs already on the market." *Id.* Dr. Madigan is a member of the FDA's Drug Safety and Risk Management Committee, which "advises the FDA Commissioner on risk management, risk communication, and quantitative evaluation of spontaneous reports for drugs for human use and for any other product for which the FDA has regulatory responsibility." *Id.* Dr. Madigan is qualified as an expert because he has "a broad range of knowledge, skills, and training [to] qualify ... [him] as such." *In re Paoli,* 35 F.3d at 741. Defendant does not dispute Dr. Madigan's qualifications.

2. Dr. Madigan's Methodology Is Sufficiently Reliable

***8** Dr. Madigan examined the FDA's Adverse Event Reporting System ("AERS") database for a "possible association between Fosamax and a series of ... terms selected by Merck to evaluate oversuppression of bone turnover and associated" AFFs. Madigan Report at ¶ 25. The terms were: bone development abnormal, bone disorder, bone formation decreased, fracture delayed union, fracture malunion, fracture nonunion, low turnover osteopathy, pathological fracture, stress fracture, fracture, and femur fracture. *Id.* at ¶ 26. Dr. Madigan used "two industry-standard signal detection algorithms ... to assess whether or not Fosamax presented a safety signal" indicating oversuppression of bone turnover or AFFs. *Id.* at ¶ 25. The QScan pharmacovigilance software computed the statistics. *Id.* at ¶ 27. Dr. Madigan then compared the Fosamax signals to other oral bisphosphonates and a non-bisphosphonate used for the treatment and prevention of osteoporosis. *Id.* at ¶ 25. After reviewing the data, Dr. Madigan opined that

> industry standard pharmacovigilance techniques and datasources reveal the presence of a clear signal for oversuppression of bone turnover and associated atypical femur fracture events utilizing the terms selected by Merck for such analysis. By standard metrics of "signal" detection, the signal is strong, consistent, and not ambiguous. Of perhaps greater concern, the signal was striking in comparison to that for other drugs indicated for the prevention and treatment of osteoporosis. As early as 2001–2002, the spontaneous report data for Fosamax provide signals for a number of indicators of suppression of bone turnover. For the comparator drugs, such signals either never appear or appear years later.
>
> [*Id.* at ¶ 36.]

This opinion is admissible because it is based on a method that is sufficiently reliable. *See Jones,* 2010 WL 3311840, at *4. Two factors that a court may take into consideration in determining reliability is whether the methodology has been subjected to peer review and publication and whether there is general acceptance in the scientific community. *Daubert,* 509 U.S. at 593–94. Here, Dr. Madigan's method, data mining in pharmacovigilance, is generally accepted in the scientific community and has "become routine both in the pharmaceutical industry and amongst regulators worldwide."

Madigan Report at ¶ 8. In fact, "[p]harmaceutical companies, health authorities, and drug monitoring centers use SRS databases for global screening for signals of new adverse events or changes in the frequency, character, or severity of existing adverse events (AEs) after regulatory authorization for use in clinical practice." *Id.* at ¶ 9. "SRS systems provide the primary data for day-to-day drug safety surveillance by regulators and manufacturers worldwide." *Id.* at ¶ 14. In addition, the QScan software Dr. Madigan used in formulating his opinion is generally accepted by the scientific community because it "has been in widespread use for over 10 years and has been validated extensively." *Id.* at ¶ 28. Moreover, "[m]any peer-reviewed publications report results derived from QScan." *Id.* Thus, Dr. Madigan's methodology is sufficiently reliable.

***9** Although Defendant argues that Dr. Madigan's methodology is unreliable because he did not review the substance of the adverse event reports to see if they actually involve AFFs or oversuppression of bone turnover, this argument is inappropriate on a *Daubert* motion. Dr. Madigan's testimony will be subject to cross-examination, and the credibility of his opinion will be ultimately determined through the adversarial process. Dr. Madigan's methodology is sufficiently reliable because it is generally accepted in the scientific community, and therefore, Plaintiffs have satisfied the second prong of *Daubert.*

3. Dr. Madigan's Testimony Fits the Facts of the Case

Lastly, Dr. Madigan's testimony fits the facts of the case and will assist the trier of fact because it is related to Plaintiffs' failure to warn claim. *See Jones,* 2010 WL 3311840, at *4. A failure to warn claim requires a plaintiff to show "(1) that a manufacturer has a duty to warn (2) against dangers resulting from foreseeable uses about which it knew or should have known and (3) that failure to do so was the proximate cause of the harm." *In re Fosamax Prods. Liab. Litig.,* 2013 WL 76140, *3 (S.D.N.Y. Jan.7, 2013). Dr. Madigan's testimony fits the facts of this case because he opines that "[a]s early as 2001–2002, the spontaneous report data for Fosamax provide[d] signals for a number of indicators of suppression of bone turnover," meaning Defendant knew or should have known that Fosamax caused certain dangers in 2001–2002, thus imposing on Defendant a duty to warn of those dangers. Madigan Report at ¶ 36.

Defendant, however, argues that Dr. Madigan's testimony does not fit the facts of the case because it is irrelevant since there is no reasonable standard of care that would have required Defendant to conduct data mining. This is also a matter best left to the credibility determination of the jury.

As a result, Dr. Madigan's expert testimony is admissible under *Daubert* because he is qualified, he used a sufficiently reliable methodology, and his opinion fits the facts of the case.

D. Dr. Blume

Dr. Blume is offered as an expert in pharmacovigilance and FDA regulation. Plaintiffs offer the testimony of Dr. Blume to: (1) "address the timeliness and completeness of the efforts undertaken by [Defendant] ... to fully inform prescribers and patients of the increasingly adverse benefit risk assessments associated with long-term Fosamax use in postmenopausal women"; (2) "evaluate the negative consequences of protracted bone oversuppression," including AFFs, in people receiving Fosamax; and (3) "to consider the pharmacovigilance activities undertaken by [Defendant] to evaluate the noted adverse events during the relevant time periods" [docket # 119, Ex. 33, Dr. Blume's Report ("Blume Report") at ¶ 6].

1. Dr. Blume is Qualified as an Expert

Dr. Blume received her Ph.D. in Pharmacology and Toxicology from the West Virginia University Medical Center and is currently the President of Pharmaceutical Development Group, Inc. (PDG), "a consulting firm ... specializing in pharmaceutical development and registration activities." *Id.* at ¶ 1. In this role, she "has been responsible for preclinical and clinical (Phases I–IV) programs associated with pharmaceutical product development and the securing of pre-marketing approvals" for many drugs before the FDA. *Id.* at ¶ 2. Additionally, Dr. Blume has directed "all phases of interactions with [the] FDA relating to the prosecution of New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), Supplements to New Drug Applications (sNDAs), and the associated approval procedures," including "the collection and evaluation of postmarketing adverse medical events, the preparation of updated product labeling, and the dissemination of accurate, complete and timely product-related information to health care providers." *Id.* at ¶ 3. She was responsible for "regulatory review of promotional and education materials for both brand-name and generic drug products." *Id.* Dr. Blume's responsibilities include the "design, execution, and interpretation of pivotal safety-related trials and the development and implementation of pharmacovigilance

procedures intended to detect new safety signals and track the evolution of previously identified signals." *Id.* at ¶ 4. She has directed "all phases of interactions with the FDA relating to post-approval labeling procedures regarding changes to safety-related information based upon postmarketing signal tracking and pharmacovigilance efforts," including "collection and evaluation of postmarketing adverse medical events, review and interpretation of the results of postmarketing clinical studies, the preparation of updated product labeling and other communication tools, and the dissemination of new product information to health care providers, patients, and consumers." *Id.* at ¶ 5. Dr. Blume possesses the knowledge, skills, and training necessary to qualify her as an expert. *See* *In re Paoli,* 35 F.3d at 741. Defendant does not dispute Dr. Blume's qualifications.

2. Dr. Blume's Methodology Is Sufficiently Reliable

***10** Dr. Blume reviewed published studies (Blume Report at ¶¶ 57–74), Merck's Period Safety Update Reports (*id.* at ¶ 75), Dr. Madigan's report (*id.* at ¶¶ 76–78), Merck's Worldwide Adverse Experience System ("WAES") (*id.* at ¶ 79), and epidemiological studies (*id.* at ¶¶ 82–90). *See also* docket # 119, Ex. 5, Dr. Blume's Deposition ("Blume Dep.") at 148:9–18; 338:9–20 (stating that she looked at the WAES database, literature reports, epidemiological studies, the AERS database, and Dr. Madigan's report). She discussed the "specific regulatory procedures and regulations" pharmaceutical manufacturers have to comply with, including procedures and regulations related to FDA approval, labeling, postmarketing surveillance, and reporting requirements. *Id.* at ¶¶ 11–34. Dr. Blume evaluated all of this information using "her years of experience" in "the industry," *see* *In re Viagra Products Liability Litigation,* 658 F.Supp.2d 950, 962 (D.Minn.2009), and opined that

> the scientific literature, Merck's internal adverse event database, the AERS database, and epidemiology analyses confirmed the increasingly adverse risk-benefit profile related to long-term Fosamax use in the indicated populations. However, Merck permitted their labeling and other prescriber information to remain static with respect to both the deteriorating risk-benefit assessment and the escalation in ... [AFF] reports. Such omissions do not comply with the regulatory and industry standards of responsible pharmaceutical companies .... Merck also should have undertaken timely and adequate studies to more clearly elucidate the risks of Fosamax use in the various indicated populations. Finally, Merck should have disseminated Dear Healthcare Professional Letters to advise prescribers and their patients of the escalating safety and efficacy concerns. Merck's omissions have likely resulted in the exposure of numerous patient populations to unnecessary risks associated with the initiation and ongoing treatment with Fosamax.
>
> [Blume Report at ¶ 110.]

Dr. Blume states that "[b]y the early 2000's, it was known that ... [AFFs] were clinically significant events ...." *Id.* at ¶ 109. Dr. Blume opines that Defendant should have changed the Fosamax label "to include escalating warning and precautionary risk information related to" AFFs. *Id.* Instead, Dr. Blume notes that Defendant "did not identify these fractures in the labeling until 2009" even though it received reports that AFFs were "associated with Fosamax use as early as 2002." *Id.* at ¶¶ 31, 82.

Defendant argues that the Court should exclude Dr. Blume's opinions on: (1) the legal requirements governing pharmaceutical manufacturers and Defendant's compliance with those requirements; (2) Defendant waiting too long to add information about femur fractures to the Adverse Reactions section of the label; (3) Defendant failing to add a warning or precaution about femur fractures to the Fosamax label before 2009; (4) Defendant's failure to timely investigate a potential link between Fosamax and AFF; (5) Defendant's alleged motives or state of mind; (6) the causation or mechanism of AFF; and (7) the drug Evista is safer than Fosamax. Yet, because *Daubert* concerns the narrow issue of whether expert testimony is admissible, this is not the appropriate time for Defendant to request that the Court preclude Dr. Blume from testifying about certain topics. Defendant may question Dr. Blume's opinions or methodology on cross-examination. *See* *Milward,* 639 F.3d at 15 (stating "[s]o long as an expert's scientific testimony rests upon "good grounds," based on what is known, ..., it should be tested by the adversarial process, rather than excluded").

***11** Despite Defendant's issues with Dr. Blume's opinions, Plaintiffs have satisfied the second prong of *Daubert* because Dr. Blume's methodology is sufficiently reliable.

3. Dr. Blume's Testimony Fits the Facts of the Case

Dr. Blume's testimony fits the facts of the case because she opines that it was known in the early 2000's that AFFs were associated with Fosamax use. *See* Blume Report at ¶¶ 31, 82.

Dr. Blume's testimony is relevant and will assist the trier of fact in deciding Plaintiffs' failure to warn claim because Dr. Blume's opinion is relevant to whether and when Defendant knew or should have known that AFFs were associated with Fosamax and therefore, when Defendant should have sought a label change. *See* *Schneider,* 320 F.3d at 404 (recognizing that expert testimony must "be relevant for the purposes of the case and must assist the trier of fact").

E. Treating Physicians

Defendant argues that the Court should preclude causation testimony from Plaintiffs' treating physicians—Drs. Busch, Lindsay, Fletcher, and Limes—because: (1) Plaintiffs have not provided Rule 26 disclosures for any of the treating physicians; and (2) none of the treating physicians are able to offer a reliable causation opinion to a reasonable degree of medical certainty. Plaintiffs, however, assert that they do not intend to elicit expert testimony from the treating physicians; instead, the treating physicians will testify about Mrs. Glynn's care and treatment, which does not require Rule 26 disclosures.

Treating "physicians are not required to submit expert reports when testifying based on their examination, diagnosis and treatment of a patient." *Patterson v. Howard,* 2010 WL 1050052, *4 (D.N.J. Mar.18, 2010). Federal Rule of Civil Procedure 26(a)(2)(B) requires a witness to submit a written report only "if the witness is one retained or specially employed to provide expert testimony in the case or one whose duties as the party's employee regularly involve giving expert testimony." A "treating physician is not necessarily retained or specially employed to provide expert testimony simply because he or she proffers on causation and prognosis" because "doctors may need to determine the cause of an injury in order to treat it." *Pease v. Lycoming Engines,* 2012 WL 162551, *12 (M.D.Pa. Jan.19, 2012). In order to "determine whether a party retained or specially employed a treating physician to provide expert testimony," the Court must examine "whether the treating physician acquired his opinion as to the cause of ... plaintiff's injuries directly through his treatment of the plaintiff." *Id.* (internal quotation omitted). As a result, treating physicians are not required to submit expert reports "if they form their opinion on causation or prognosis as part of the ordinary care of a patient." *Id.*

Therefore, the testimony of Drs. Busch, Lindsay, Fletcher, and Limes is appropriate if it is based on their care and treatment of Mrs. Glynn. This Court will not allow, however, any expert testimony on causation from these physicians.

II. CONCLUSION

***12** For the reasons outlined above, this Court denies Defendant's *Daubert* Motion as to Drs. Cornell, Klein, Madigan, and Blume. An appropriate Order accompanies this Opinion.

All Citations

Not Reported in F.Supp.2d, 2013 WL 1558690, 91 Fed. R. Evid. Serv. 106

Footnotes

1 The abbreviation of atypical femur fracture (singular) is "AFF."

2 Db13 means page 13 of Defendant's brief.

3 Pharmacovigilance is the surveillance of spontaneous reporting system ("SRS") databases "for the early detection of drug hazards that are novel by virtue of their clinical nature, severity, and/or frequency." *Id.* at ¶ 7.

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